The Pharmacology and Clinical Use of Diuretics

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The Pharmacology and Clinical Use of
DIURETICS

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PREFACE

The discovery by Vogel that the organic mercurial merbaphen (Novasurol) produced diuresis initiated extensive studies on the effects of such compounds that have continued up to the present time. Early in their studies, Saxyl and Heilig established that the effect of merbaphen consisted in a massive excretion of sodium chloride accompanied by a large volume of water. They further observed that the ingestion of excessive amounts of salt interfered with the diuretic action. The same investigators found that the parenteral administration of other mercurial compounds, available at the time, were not diuretics They, therefore, concluded that diuresis was due to the organic mercurial as such and not due to the release of inorganic mercury.

Following in the wake of the observations on the diuretic activity of merbaphen, a number of new organomercurial compounds were prepared. Some of these agents were much less toxic and better tolerated than merbaphen. The development of the superior mercurials used today have a comparatively short history and new agents are constantly being introduced.

Up until recently, diuretic therapy has centered largely around the mercurial compounds. In recent years, numerous non-mercurial diuretics for oral use have appeared. These agents will probably never entirely replace the mercurial compounds, but do appear to have an important place in diuretic therapy.

Much of the data presented in this volume are derived directly from the experience of the authors over the past

ten years with a number of diuretic compounds. No attempt has been made to present a comprehensive review of the literature.

CARROLL A. HANDLEY
JOHN H. MOYER

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The Pharmacology and Clinical Use of Diuretics

Chapter 1

RENAL REGULATION OF WATER AND ELECTROLYTE EXCRETION*

ALTHOUGH WATER and electrolytes are lost through the skin and gastrointestinal tract, the kidneys are largely responsible for maintaining the volume and composition of body fluids. There are several coordinated mechanisms responsible for this renal regulation.

Water balance. The maintenance of a nearly constant volume of water in the several fluid compartments of the body, under normal conditions, is largely controlled by the antidiuretic hormone (ADH) but other hormones are also involved. Different processes are believed to be involved in the reabsorption of water by the kidney in the proximal and the distal tubules. Available evidence indicates that approximately 85 per cent of the glomerular filtrate is returned to the peritubular blood from the proximal tubules by simple diffusion (97). More than 99 per cent of the remainder of the filtered water may be reabsorbed in the distal tubule by an active process requiring ADH to function. This latter mechanism makes it possible for the kidney to return water to the circulating blood against an osmotic gradient.

The secretion of ADH is regulated by changes in concentration of sodium chloride in the extracellular fluid and therefore in the plasma (105). Verney has demon-

*Aided by a grant from the American Heart Association, Inc.

strated that end organs, similar to the pressor receptors of the carotid sinus, are located in certain of the blood vessels supplying the brain. These organs are referred to as osmoreceptors. Hydration, of sufficient degree to only slightly reduce the plasma concentration of sodium chloride, causes the osmoreceptors to swell which reduces the output of ADH. This results in an increased output of water with little change in salt excretion. The extra water is thus eventually eliminated. Under normal conditions, water intake usually exceeds requirements and a balance is maintained by renal excretion of the surplus. The reestablishment of an isotonic plasma after excessive water intake is then largely due to the functional linkage between the neurohypophysis and the kidneys.

During a period of dehydration, a converse chain of events takes place. If water is withheld, the extracellular fluid becomes hypertonic, since water is lost through the urine, lungs and skin without a parallel salt loss The osmoreceptors respond by stimulating the neurohypophysis to secrete increased amounts of ADH. As this hormone accumulates in the cells of the renal tubules, the kidneys conserve water by reabsorbing more and secreting a more concentrated urine. However, complete compensation cannot be effected during water deprivation because unavoidable water losses continue through the skin, lungs and the minimum urine volume necessary to excrete waste products.

Electrolyte balance. Normally, sodium chloride balance is maintained by the kidneys in a manner similar to the maintenance of water balance. Average daily intake exceeds requirements and the excess is excreted in the urine. The body conserves salt much more efficiently than water. When neither food nor water is ingested, water depletion is

the dominant picture. When water alone is administered, it requires a considerable period of time, in the absence of abnormal salt loss, before serious depletion occurs. The kidneys practically cease to excrete salt under these conditions as was demonstrated many years ago by Benedict. To maintain a constant sodium chloride concentration in the extracellular fluid requires that the urine may sometimes contain more, less or an equivalent amount of salt as the plasma.

At a glomerular filtration rate (GFR) of 120 ml per minute and a plasma sodium concentration of 140 mEq per liter, the sodium filtered per minute will be about 17 mEq. Since the rate of sodium excretion per minute usually varies between 0.05 and 0.5 mEq per minute, it is apparent that much of the filtered sodium is reabsorbed as is the case with filtered water. During an average day about 24,000 mEq of sodium are filtered, but the urinary output is likely to be only 450 mEq or less. Similarly, from the 170 liters of water filtered per day, 2 liters or less of urine are formed. Normally, the regulation of the renal reabsorptive mechanisms are such that the concentration of sodium and chloride in the fluid reabsorbed is nearly identical with that of the extracellular fluid Probably similar undisclosed renal mechanisms operate to regulate the concentration of other constituents of the glomerular filtrate in the fluid reabsorbed Figure 1 is a diagram of possible segments of the nephron where changes in the composition of glomerular filtrate occur.

Mechanisms controlling sodium reabsorption. Of the sodium present in the glomerular filtrate, about 85 per cent is said to be reabsorbed by the cells of the proximal tubule. Since a similar amount of water is reabsorbed by this segment of the nephron, the fluid of the proximal tubule is thought to remain isotonic or slightly hypotonic.

The glomerular filtrate is presumably a fluid of the same electrolyte composition as extracellular fluid, which is in equilibrium with cell fluid. Because of the absence of a

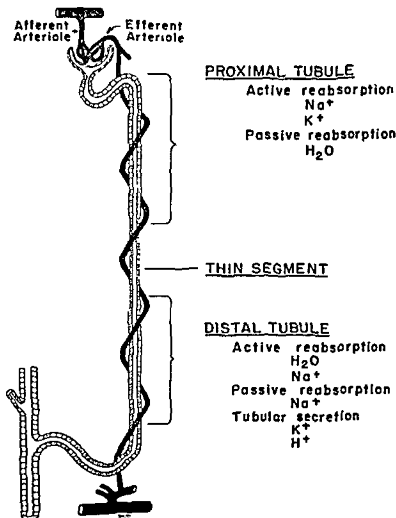


Figure 1. Schematic diagram of water and electrolyte reabsorption from glomerular filtrate in the nephron

favorable osmotic gradient, when the filtrate first enters the tubule, the transfer of sodium from tubular fluid to the tubule cells in the proximal tubule must be an active process involving the expenditure of energy. Water then follows passively due to osmotic pressure difference between intratubular and peritubular fluids which have been established by prior reabsorption of solutes. In the distal tubule, active reabsorption of water occurs under the influence of ADH. There are proponents of the theory that a mechanism exists for the active reabsorption of sodium, activated by adrenal cortical steroids (97), in this segment, although passive sodium reabsorption in this part of the nephron has not been excluded.

Recently, work has indicated that ion exchange mechanisms exist in the cells of the renal tubules which are involved in the reabsorption of sodium (4,85). Hydrogen, potassium and ammonium ions are believed to be secreted into the tubule lumen in exchange for sodium ions. The location in the nephron and the control of these exchange mechanisms have not been establishd.

Hormonal control of sodium reabsorption. The active reabsorption of the small but significant fraction of sodium that probably occurs in the distal tubule is believed to be controlled by the adrenal cortical steroids. Some confusion has been created by the extensive studies with desoxycorticosterone, a synthetic compound that probably has no physiological counterpart. One important difference between desoxycorticosterone and adrenal cortical extract is that the former is salt-retaining at all levels of plasma sodium. On the other hand, cortical extracts are salt-retaining at low plasma levels of sodium, but may actually increase the output of salt when the plasma sodium concentration is elevated. Nevertheless, the value of desoxy-

corticosterone in the treatment of the electrolyte imbalance of Addison's disease is well-established.

The recent discovery that the adrenal venous blood of mammals contains a steroid which is many times more potent than desoxycorticosterone in controlling renal electrolyte excretion resulted in the isolation and identification of aldosterone. It is approximately 30 times more potent than desoxycorticosterone as a salt-retaining hormone. Although hydrocortisone may be present in larger amounts in adrenal venous blood of dog and man, aldosterone would appear to have a dominant action on electrolyte excretion because of its greater potency (96). There is evidence to indicate that its secretion varies according to requirements for electrolyte balance. In normal men, sodium restriction increases the output of the hormone and reduces urine sodium. After resumption of a normal sodium intake, the excretion of both hormone and sodium return to control levels (53).

Mechanisms causing the release of aldosterone. Although the mechanism that controls the release of aldosterone is uncertain, the concentration of sodium in the extracellular fluid, the concentration of potassium and blood volume have all been implicated (10) Unlike the other cortical steroids, the release of aldosterone appears to be independent of corticotropin (ACTH).

The site of action of the cortical hormones remains undetermined Certainly, their effects on renal transfer mechanisms must be a reflection of an action on the cells of the renal tubules. Shifts in water and electrolytes that cannot be explained on the basis of renal effects suggest that other tissue cells are also affected

The effect of cortical hormones on the excretion of other ions. It is commonly stated that the cortical hor-

mones and ACTH, through its influence on cortical hormone secretion, cause a renal retention of sodium and water and a loss of potassium. Actually, these hormones may decrease the elevated plasma potassium level after adrenalectomy of animals without increasing urinary excretion of this ion. Such observations indicate that cellular shifts of potassium as well as a decreased rate of excretion are involved in the hyperkalemia of adrenal insufficiency. Nevertheless, cortical hormones are effective in promoting potassium excretion and may even produce hypokalemia.

The effect of renal hemodynamics on sodium excretion. Interest in the relationship of hemodynamic factors on sodium and water excretion was aroused by the postulate that sodium retention in edema of heart failure may result from a decrease in cardiac output. This, in turn, would reduce renal blood flow and glomerular filtration rate. The lower volume of filtrate, and hence sodium, presented to the tubules under these conditions was thought to result in more complete reabsorption (60, 102). There is ample evidence that acute reductions in blood pressure may be associated with a decrease in glomerular filtration rate, urine volume and sodium excretion, in both animals and man (46, 78, 94—see Figure 2 and Table 1). These changes occur from hemorrhage or drug-induced hypotension. Conversely, elevation of blood pressure from a hypotensive to a normotensive level by infusion of a vasoconstrictor agent usually results in improvement in renal functions, including the rate of water and sodium excretion.

The above results should not be inferred to indicate that changes in glomerular filtration rate is an important regulatory mechanism for sodium and water excretion. On the contrary, changes in active reabsorption of water and sodium in the renal tubules appear to be the impor-

tant mechanisms for maintaining a constant volume and composition of body fluids. Conditions associated with a chronic reduction in glomerular filtration rate, such as hypophysectomy in dogs and from various causes in man, are not necessarily associated with an abnormal fluid and electrolyte balance. Indeed, in Addison's disease there is excessive salt and water loss even though the glomerular filtration rate is considerably reduced.

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Chapter 2

POSSIBLE MECHANISMS OF ELECTROLYTE AND WATER RETENTION IN DISEASES AMENABLE TO DIURETIC THERAPY

CONGESTIVE HEART FAILURE

THE EXACT mechanism or mechanisms causing a retention of salt and water in heart failure is still in doubt, although considerable effort has been and still is directed toward the solution of this problem. As the dominant ion of the extracellular fluid, sodium, and its associated anions assume great importance in the regulation of body fluid volume. An increase in renal tubular reabsorption of as little as one per cent of filtered sodium per day would mean the gain of about 11 grams. This would result in the retention of more than three liters of water to maintain the normal osmolarity of the extracellular fluid.

In the sodium retention and edema associated with congestive heart failure, the kidney has long been implicated. A number of physiological changes have been proposed as causative factors responsible for the inability of the kidneys of these patients to maintain normal electrolyte and water balance. Some of these are discussed below.

The influence of glomerular filtration rate. Acute reduction in glomerular filtration by ganglionic blocking agents such as trimethaphan (Arfonad) can depress sodium

excretion (Figure 2) and a reduction in glomerular filtration rate has been proposed as one factor contributing to edema formation in congestive heart failure. This is based on the observation that patients in failure often have a reduced renal plasma flow and glomerular filtration rate (Figure 3). In a study on the effect of mild exercise on glomerular filtration, the filtration rate of the majority of cardiac patients examined fell well below the 70 cc per minute rate that was considered the critical level for sodium retention (60). The explanation for the development of edema under these circumstances is that with a reduced

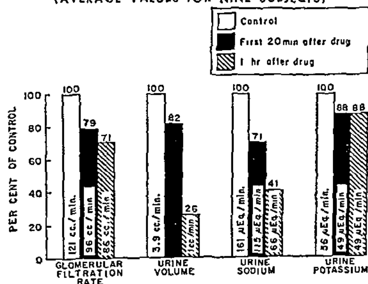


Figure 2. *The effect of blood pressure reduction* with the ganglionic blocking agent trimethophan (Arfonad) on glomerular filtration rate, water and electrolyte excretion.

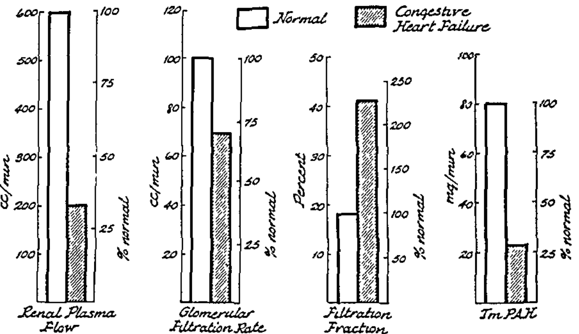


Figure 3. In congestive heart failure, glomerular filtration rate, renal blood flow and tubular function are frequently depressed. (After Ford and Moyer (25), courtesy G/P.)

volume of filtrate, it passes down the tubules more slowly. This increases the time during which the fluid is in contact with the cells of the tubules and results in an increased amount of sodium and water reabsorption (97).

Considerable disagreement exists as to what extent filtration rate alone influences sodium retention Indeed, many investigators disclaim any correlation between filtration rate and the rate of sodium excretion. Certainly, the filtration rate cannot be the only factor, since numerous cases have been recorded in the literature with filtration rates well below the supposed critical level without the development of edema. Furthermore, a number of investigators have pointed out that while acute reductions in filtration rate may decrease the rate of sodium excretion, there is frequently a definite and marked time lag between the restoration of filtration rate to normal levels and a resumption of control rates of sodium excretion. This might occur from reduced filtration rates caused by tilting (Table I), by vascular obstruction, or by a pneumatic cuff about the thigh. Other longer term studies have demonstrated no relationship between recovery from congestive heart failure and changes in filtration rate.

The influence of cardiac output and venous pressure on sodium and water retention. Several investigators have proposed that the retention of sodium in congestive heart failure is directly related to a reduction in cardiac output (9,101,108). It must be conceded that renal hemodynamic changes resulting from a reduction in cardiac output can result in sodium retention and edema. However, other mechanisms must also operate to explain the heart failure and edema that may occur with a high cardiac output associated with anemia or chronic emphysema.

TABLE I

THE EFFECT OF SIXTY DEGREE TILT ON RENAL FUNCTIONS, URINE VOLUME AND ELECTROLYTE EXCRETION

(After Ford, Moyer and Spurr (30), courtesy *American Heart Journal*)

	*MBP**	*GFR** *cc/min*	*RPF** *cc/min*	*TmPAH** *mgm/min.*	*U.V.** *cc./min*	*Na** *mgm./min.*	*K** *mgm/min.*
‡ Control	141	80	435	59	8.6	9.7	3.1
Tilt	126	51†	291†	47†	4.1†	3.5†	1.8†
% Control	90	71	72	82	50	40	75

* Average values
† Statistically significant
‡ The control and tilt comprise 20 patients
MBP = Mean blood pressure
GFR = Glomerular filtration rate
RPF = Renal plasma flow
TmPAH = Maximum renal tubular secretory rate for p aminohippurate
U.V. = Urine volume

Acute elevation of venous pressure in experimental animals has been demonstrated to cause sodium retention. Experimentally, chronic changes in renal venous pressure do not uniformly result in edema unless hepatic venous congestion has been induced simultaneously. These observations may indicate that any effects a high venous pressure may have on sodium rentention is due to effects other than a direct action on the kidney.

Humoral factors and sodium retention. The steroid hormones of the adrenal cortex have long been known to exert a powerful influence on electrolyte excretion. Figure 4 shows the effects of a fluorinated derivative of hydrocortisone. Aldosterone, the most recently discovered of the salt-retaining steroids, has been detected in adrenal venous blood of dogs and monkeys and in the urine (19). While hydrocortisone may be present in a higher concentration in the peripheral blood of dog and man, aldosterone dominates the steroids released in terms of its effect on electrolyte excretion. The powerful effect of the synthetic steroid desoxycorticosterone in increasing renal tubular sodium reabsorption stimulated the search for increased rates of excretion of salt-retaining steroids in the urine of edematous patients. These investigations led to the discovery of aldosterone (53).

Aldosterone is present in detectable amounts in normal urine. Increased amounts of the steroid appear in the urine of normal man during sodium restriction. The increased steroid excretion is correlated with the reduction in urinary sodium excretion during the period of low sodium intake and returns to normal levels as sodium excretion increases after resumption of a normal diet. These reciprocal changes in aldosterone and sodium excretion in the urine are not accompanied by significant

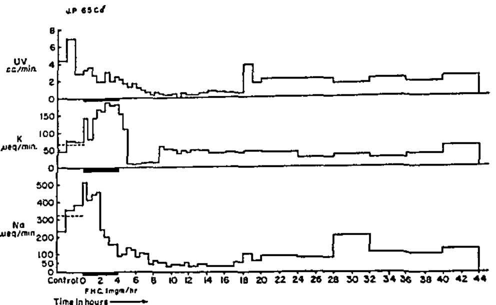


Figure 4 *The effect of fludrocortisone acetate (9 fluorohydrocortisone) on water and electrolyte excretion.* (After L. C. Mills, unpubished data)

alterations of glomerular filtration rate or urinary excretion of 17-keto steroids or 17-hydroxycorticoids. This inverse relationship between sodium excretion and aldosterone output is also seen in patients developing edema and during subsequent diuresis, either spontaneous or induced. These observations have led to the tentative proposal that aldosterone is the adrenal cortical steroid responsible for maintaining normal sodium and potassium balance and may be an important factor responsible for sodium retention and edema in congestive heart failure. It should be emphasized that there is not yet any clear-cut evidence for a causal relationship between an increased aldosterone excretion and the development of edema in heart failure.

Although the mechanism of sodium retention in cardiac failure is still controversial, its importance is clearly demonstrated by the therapeutic success of measures used for circumventing it, such as diuretics and a low-sodium diet. Electrolyte retention also causes stimulation of hypothalamic osmoreceptors which results in the secretion of additional antidiuretic hormone (ADH). The hormone may be responsible for further water retention associated with increased blood volume and increased venous pressure leading to the formation of more edema fluid. Other hormonal changes may also be involved in the development of edema. The reduction in water and electrolyte excretion by the kidneys is the one obvious overall effect causing the formation of edema fluid of congestive heart failure.

The management of congestive heart failure is one area that has been significantly improved by the judicious application of pharmacologic principles. Figure 5 is a graphic demonstration to illustrate how several different

mechanisms may be involved in abnormal sodium and water retention in cardiac failure (60). The final common pathway is direct and indirect effects on the kidney resulting in abnormal tubular reabsorption of sodium and water. Therapy is therefore directed toward improvement in myocardial function as well as a partial blockade of the sodium and water reabsorption in the kidney.

PREMENSTRUAL EDEMA AND EDEMA ASSOCIATED WITH PREGNANCY

The regular occurrence of mild generalized edema in a large percentage of women during menstruation has been reported by many investigators. In a study on a large number of normal women during the menstrual cycle, two periods of weight gain were observed (104). Approximately 50 per cent of the group studied gained 1 kgm (2.2 lbs.) or more during the premenstrual period. Seventy-five per

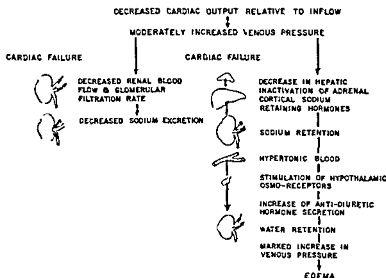


Figure 5. Some of the possible factors that may be involved in the genesis of edema.

cent gained 1 kgm or more at or about the time of ovulation. Menstruation and the postmenstrual period were associated with weight loss.

A striking symptom noted in many women premenstrually is an increase in appetite and thirst. Increased food and water consumption are apparently largely responsible for the weight gain, since it can be prevented by controlling diet and fluid intake. During the periods of the menstrual cycle when weight is gained, the urine volume and sodium excretion are reduced. As weight is lost postmenstrually, a diuresis occurs.

It is known that in normal women the highest concentration of estrogens in the urine occurs at or about the time of ovulation. A second increase in estrogen excretion occurs premenstrually. The observed correlation between increased estrogenic excretion and weight gain suggests that these hormones might resemble the salt-retaining steroids of the adrenal cortex A study of several purified estrogens showed them all to have salt-retaining action in dogs. Among the preparations studied, estrodiol was the most potent in depressing sodium excretion, although it is much less active than desoxycorticosterone.

It seems likely that the estrogens act directly on the cells of the renal tubules as the adrenal cortical steroids probably do to promote sodium retention. Injections of estrogen into women have been observed to produce a significant reduction in sodium and chloride excretion in the absence of changes in glomerular filtration rate and renal plasma flow.

The problem of premenstrual edema has received more attention from the practicing physician than it has from the investigator and has been recognized as a syn-

drome associated with sodium and water retention resulting from hormonal imbalance. The edema which presents itself is thus amenable to relief by dietary restriction of salt and the administration of natriuretic agents.

Edema in pregnancy may be seen as an exaggeration of a pre-existing disease such as congestive heart failure, nephritis, etc., or it may be a manifestation of an impending toxemia of pregnancy. It should be remembered, however, that even during normal pregnancy the blood volume increases about 50 per cent (13,16) and that there is a positive salt balance (retention of salt and water) reaching a maximum by the thirty-sixth week of gestation. The influence of an enlarged uterus producing increased pressure on intra-abdominal veins may be an important contributory factor. Whatever the complex and interrelated factors may be, the common denominator is, once more, increased tubular reabsorption of sodium and water which can be corrected by appropriate therapy.

NEPHROTIC SYNDROME

One might assume that the edema frequently associated with the nephrotic syndrome is directly attributable to the low plasma albumen concentration. In this disease, large quantities of albumen are lost in the urine It is generally assumed that the permeability of the glomerular capillaries is so altered that albumen escapes from the plasma in the filtrate while the larger globulin molecules are retained. The urine contains large amounts of albumen and the total plasma protein concentration is reduced to 3 5 to 5.3 per cent. Plasma globulin concentration is normal or even above normal due to an increased rate of formation.

Normally, the capillary membrane is permeable to all plasma constituents except proteins and lipids. The formation of edema fluid results from an imbalance of the forces that regulate the exchanges of fluid between plasma and extracellular fluid. The hydrostatic pressure resulting from cardiac contraction is opposed by the osmotic pressure of the plasma proteins. Fluid is forced out at the arterial end of the capillaries since the hydrostatic pressure tending to force fluid out is greater than the colloid osmotic pressure tending to retain fluid in the capillaries. As the venous end of the capillary is approached, the conditions for fluid exchange are reversed. An amount of fluid approximately equal to that forced from the capillary is returned to the circulating blood. Normally, these opposing forces are delicately balanced so that the volume of plasma and extracellular fluid remain relatively constant. A reduction in plasma albumin, such as occurs in the nephrotic syndrome, would favor the development of edema. However, hypoproteinemia cannot be the sole factor responsible for the edema of this disease since diuresis and loss of edema may occur spontaneously while the plasma protein concentration remains low (91). Also, it has been observed that repeated administration of concentrated serum albumin, to increase the plasma albumin concentration, frequently fails to relieve the edema in patients with nephrosis (58).

The plasma volume may be reduced as much as 20 to 30 per cent during the development of edema because of the diversion of water and solutes to the interstitial compartment. Reduction of plasma volume has been found to be accompanied by a decrease in renal plasma flow and filtration rate. Expansion of the plasma volume by albumin administration produces moderate increases

in the filtration rate in most patients (22). A good correlation between the increased filtration rate and an increased rate of salt and water excretion was demonstrated in this study. Failure to achieve diuresis following albumin administration correlated with failure to increase the filtration rate in spite of plasma volume expansion.

Despite the observed correlation between filtration rate and diuresis, edema may occur in nephrotic patients who have normal or even supernormal filtration rates. This has been ascribed to an increased rate of sodium absorption by the renal tubules.

Sodium retention due to the secretion of increased amounts of adrenal-cortical steroids may be one of the

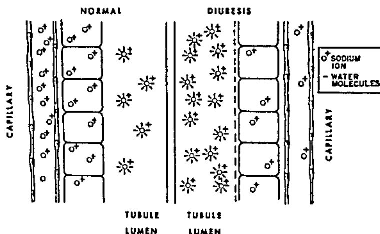


Figure 6. Schematic diagram to show partial blockade of sodium and water reabsorption by diuretics. This is the common denominator which makes diuretic (natriuretic) agents effective in a wide variety of clinical syndromes of diverse etiology.

factors causing the edema of nephrosis. Increased amounts of aldosterone have been found in the urine of edematous patients with nephrosis (53). If this steroid is a contributory factor to the retention of electrolytes and water in these patients, the stimulus for its release remains unknown.

In the treatment of the nephrotic syndrome, there is not only a need for a natriuretic agent but frequently better results may be obtained by an agent which increases the plasma colloid osmotic pressure, such as salt-poor human albumin administered intravenously Albumin sometimes appears to also have a natriuretic and diuretic effect on the kidney which is unrelated to its osmotic effect.

HEPATIC DISEASE

Hepatic disease presents the problem of disordered protein formation which results in a decreased colloid osmotic pressure of plasma. The plasma proteins may be sufficiently low to warrant the administration of salt-poor human albumin. Decreased inactivation of salt-retaining steroids, due to poor liver function, may be a contributory factor to sodium and water retention. At the present stage of our knowledge, this condition can only be controlled by a natriuretic agent. Indirectly, diuretic therapy may actually conserve proteins in these patients by either eliminating or increasing the interval between paracenteses.

IATROGENIC STEROID EDEMA

We have labeled the increasingly common syndrome resulting from the therapeutic use of steroids such as

cortisone, hydrocortisone, prednisolone and prednisone "steroid edema" since it is one of the iatrogenic forms. In this condition, edema is induced by increased renal tubular reabsorption of sodium. Diuretic agents, particularly the organomercurials, have been especially helpful in the management of this complication.

In discussing some of the more common clinical syndromes associated with edema, we have seen that many factors may be involved and that the exact contribution of each to the genesis of edema cannot at present be defined. It is not unlikely that in the near future an orderly progression of events leading to the development of edema will emerge from the chaotic state that now prevails Nevertheless, whether or not the kidneys are directly or indirectly involved, the empirical use of diuretics is a recognized and valuable therapeutic measure in these conditions.

TABLE II

SOME CLINICAL SYNDROMES ASSOCIATED WITH EDEMA FOR WHICH DIURETIC AGENTS ARE USED

Clinical Disorder	*Possible Mechanisms of Edema Formation*	*Therapeutic Approach**	*Primary Pharmacodynamics of Therapy*
(1) Congestive Heart Failure	Increased venous pressure with decreased blood flow to kidneys and liver, resulting in retention of sodium and water Osmoreceptors stimulation with retention of water. Increased secretion of salt-retaining steroids	Digitalis preparations Natriuretic agents Low sodium intake	Improved cardiac function Decreased renal tubular reabsorption of sodium
(2) *Premenstrual edema*	Abnormal hormonal balance with renal tubular retention of sodium	Natriuretic agents	Decreased renal tubular reabsorption of sodium
(3) Edema of Pregnancy	Increased abdomino pelvic pressure. Hormonal imbalance	Natriuretic agents	Decreased renal tubular reabsorption of sodium.
(4) Nephrotic syndrome	Excessive loss of protein. Decreased glomerular filtration and renal blood flow Increased secretion of salt retaining steroids	Osmotic diuretic Natriuretic agent Anti inflammatory steroids	Increased blood osmotic pressure Increased renal water loss Decreased renal tubular reabsorption of sodium Increased glomerular filtration rate and improved tubular function
(5) Hepatic disease	Disordered protein formation. Decrease inactivation of salt-retaining steroids	Osmotic diuretic Natriuretic agent	Increased blood osmotic pressure Decreased renal tubular reabsorption of sodium
(6) "Steroid edema"	Increased tubular reabsorption of sodium	Natriuretic agent and reduce steroid intake	Decreased renal tubular reabsorption of sodium

* The low sodium dietary regimen is common to all therapeutic programs

Chapter 3

CLINICAL BIOASSAY AND POTENCY ESTIMATION OF DIURETICS

A BETTER UNDERSTANDING of the mechanisms causing salt and water retention has led to a more extensive use of diuretics. This, in turn, has resulted in the introduction of a number of new compounds, which has created a need for a reliable method for establishing the relative potency of these agents. We have directed our attention toward the development of such a method (33).

Hospitalized patients were studied under controlled conditions so that their water and electrolyte balances could be established. Initial observations indicated that the acute response to mercurial diuretics in normal individuals and in patients with congestive heart failure did not differ significantly, as indicated by the excretion of sodium. This is illustrated in Figure 7. It may be seen that the degree of increase in sodium excretion in the cardiac and the non-cardiac (maintained on a 150 mEq sodium diet) is similar. The response, is, however, influenced by the sodium content of the diet. It therefore became necessary to establish the effect of the dietary sodium before proceeding with the determination of the relative potency of different diuretics. Figure 8 shows potency estimations of a diuretic agent in terms of changes produced in sodium, chloride, and water excretion and body weight when the patient was maintained

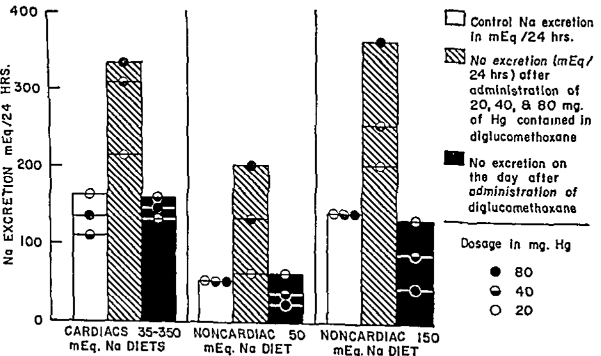


Figure 7. Comparison of sodium excretion after the administration of *various doses of a* diuretic to a non-cardiac patient and to a group of patients in cardiac failure Note the low rate of sodium excretion after the diuretic in the non-cardiac patient on a low sodium (50 mEq) diet (After Ford, Spurr and Moyer (33), courtesy *AM & CT*)

on two different diets. On higher sodium intake, the diuretic agent produced 1.8 times as great an increase in sodium excretion as that observed with the diet containing only 50 mEq of sodium. Similar differences were observed for chloride and excretion of water and weight.

Next, the reliability of the various observed responses had to be evaluated. This was done by the use of fiducial limits. The narrower the range of the limits, the more reliable the results (Table III). For sodium and chlo-

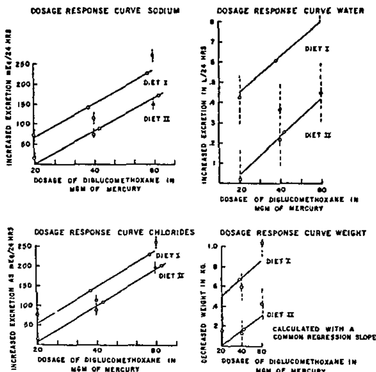


Figure 8 The dosage-response curves for Diet I (150 mEq of sodium per day) are greater than the curves for Diet II (50 mEq of sodium per day) (After Ford, Spurr and Moyer (33), courtesy *AM & CT.*)

ride excretion, the fiducial limits are quite small (1.5 to 2.2 for sodium), whereas the fiducial limits of water are fairly wide (1.8 to 12.6). This indicates that the most reliable method for comparing potency of mercurial diuretics is to note their effects on sodium or chloride excretion.

Utilizing these principles, dosage response curves were determined for various diuretics (Figure 9). All drugs were administered parenterally with the exception of chlormerodrin which was given orally. Calculated potency estimations for these agents are presented in Table

TABLE III

POTENCY ESTIMATIONS OF DIETARY SODIUM USING DIET II* AS A STANDARD (After Ford, Spurr and Moyer (33), courtesy *Antibiotic Medicine and Clinical Therapy*)

Function	*Potency Estimation*
Sodium	RL = 1.5 R = 1.8 RU = 2.2
Chlorides	RL = 0 1 R = 1.4 RU = 1 7
Water	RL = 1.8 R = 2 8 RU = 12 6
Weight	RL = 1.7 R = 2.4 RU = 4 2

* Diet I = 150 mEq Na. Diet II = 50 mEq Na

R is the best estimate of the potency of Diet I (150 mEq Na) compared to the standard, Diet II (50 mEq Na)

RL, RU = Lower and upper 5% fiducial limits (calculated by Fieller's theorem)

R means that 1 mgm. of diglucomethoxane (Mersoben) given at a diet level of 150 mEq Na/day is as effective as 1.8 mg diglucomethoxane when given at a diet level of 50 mEq/day in producing increased output of sodium.

IV. When increased sodium excretion is used as a basis for comparison and meralluride is chosen as the "standard" with a potency of *one*, mercaptomerin has a relative potency of 0.6 (60 per cent as potent), orally administered chlormerodrin, a potency of 0.5 and diglucomethoxane, a potency of 1.3 (Table IV).

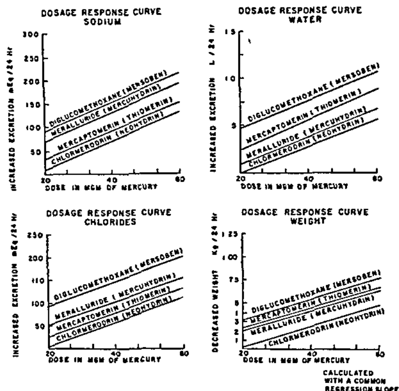


Figure 9. Dosage-response curves obtained with five different mercurial diuretics. The curves show parenteral Neohydrin to be the most potent. Orally administered Neohydrin is within the same potency range as Thiomerin. (After Ford and Moyer (33), courtesy *AM & CT*.)

The following conclusions may be drawn from our bioassay study of mercurial diuretics:

1. The response to a diuretic is directly proportional to the dose, and dietary sodium content. The most *significant change seems to be the increase in sodium (and* chloride) excretion while other changes (weight and water) are secondary.

2. Changes in the rate of sodium excretion furnish the most reliable estimate of potency of diuretics in general (exception: chloride is slightly better for mercurial diuretics).

TABLE IV

POTENCY ESTIMATIONS OF MERCURIAL DIURETICS AS COMPARED TO A STANDARD – MERALLURIDE (MERCUHYDRIN*). (After Ford, Spurr and Moyer (33), courtesy *Antibiotic Medicine and Clinical Therapy*.)

	Thiomerin P† (*Mercaptomerin*)	*Neohydrin O†* (*Chloromerodrin*)	*Mersoben P†* (*Diglucomethoxane*)
Sodium	RU = 2.4 R = 0 6 RL = 0 3	RU = 0 9 R = 0.5 RL = 0 5	RU = 2.3 R = 1.3 RL = 0.7
Weight	RU = 3 8 R = 0 9 RL = 0 4	RU = 1 9 R = 0 7 RL = 0 1	RU = 6 0 R = 1.5 RL = 0.5
Chlorides	RU = 1 2 R = 0.7 RL = 0 4	RU = 1 1 R = 0 6 RL = 0 3	RU = 3 4 R = 1.8 RL = 1 1
Water	RU = 4.5 R = 1.3 RL = 0 7	RU = 1.8 R = 0 8 RL = 0 3	RU = 9 6 R = 2 6 RL = 1.2

* 1 mgm. of Drug II (etc.) is equivalent in action to R mgm of the standard, e g , 1 mgm. Thiomerin = 0 6 mgm Mercuhydrin as a natriuretic agent and 0 7 mgm. Mercuhydrin as a chloruretic agent

R is the best estimate of the potency of Drug II with respect to the standard, Drug I (Mercuhydrin)

RU and RL are upper and lower 5% fiducial limits on this estimate of potency. (Calculated according to Fieller's theorem.)

† P and O indicate the parenteral and oral forms of the drug respectively.

Carbonic anhydrase inhibitors present a specific problem in potency estimation since it is difficult to establish a dosage response curve (34). However, a maximum effective dose can be determined when very small doses are administered in a log dose incremental fashion until further increases in dosage result in no further increase in the excretion rate of sodium. This point was arbitrarily termed the "apex" of the curve. Figure 10 shows such a curve obtained with ethoxzolamide (Cardrase). There was a minor increase in the excretion rate for sodium at the small dose tested (33.75 mgm) followed by an increasing magnitude of response until the 125 mgm dose was reached. At this dose the curve flattened out and became parallel to the base line. This same procedure was used also for the establishment of the "apex" doses for acetazoleamide (Diamox) and Butamide. The "apex" point for each of these three drugs was similar except that Butamide was slightly more potent. At least two times that dose at the "apex" was administered as the testing dose for each of the drugs (Figure 10). With acetazoleamide (Diamox) and ethoxzoleamide (Cardrase), the dosage for each test of potency was 250 mgm daily and for Butamide it was 150 mgm, since its "apex" dose was 75 mgm.

In Table 5, the increased rates of excretion of sodium, electrolytes, and water, as well as the decrease in weight, following the administration of acetazoleamide and two other carbonic anhydrase inhibitors are recorded. The figures are based on averages of two consecutive days when comparative test doses (twice the maximum effective dose for each) of the drugs were administered. There was an average increase in the urinary excretion of sodium and potassium of 35 mEq per 24 hours with

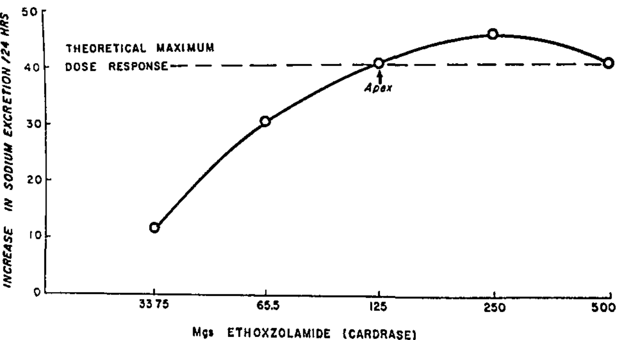


Figure 10. The "apex" point of a carbonic anhydrase inhibitor. (After Ford, Spurr and Moyer (34), courtesy *Circulation*.)

acetazoleamide. The chloride excretion rate decreased by 9 mEq per 24 hours. Water excretion increased by 0.44 liters per 24 hours and the weight decreased by 0.3

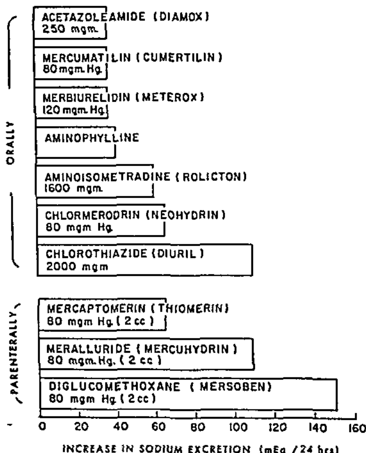


Figure 11. Comparative potency of different diuretics (After Ford, Spurr and Moyer (34), courtesy of *Circulation*)

TABLE V

SUMMARY OF THE AVERAGE EFFECT ON BODY WEIGHT AND THE EXCRETION RATES OF WATER AND ELECTROLYTES (After Ford, Spurr, and Moyer (34), courtesy of *Circulation*)

	Increased Sodium Excretion (MEq/24 hrs)	*Increased Potassium Excretion (mEq/24hrs)*	*Decreased Chloride Excretion (mEq/24hrs)*	*Increased Water Excretion (liters/24 hours)*	*Weight Loss (kgms.)*
Acetazoleamide (Diamox)	35*	35*	− 9†	0.14*	−0.3‡
Ethoxzolamide (Cardrase)	44*	37*	− 6	0.43†	−0.6†
Butamide	31*	43*	−11	−0.20§	−0.2§

* − $p < 0.001$
† − $p < 0.01$ Statistically significant
‡ − $p < 0.02$
§ − $p < 0.05$

kilograms per 24 hours. The increase in the excretion rate of sodium per 24 hours was 44 mEq for ethoxzolamide and 31 mEq for Butamide. It should be noted that changes in the excretion rates of potassium, chloride, and water as well as for the change in weight were similar for these three drugs.

The significance of this data has been established by the analysis of variance. Application of student's "t" test to the changes following each drug further shows that the increases for the excretion of sodium, potassium, and water are significant as well as the change in weight, but that the changes in chloride excretion are of border line significance. Previous experimental data has indicated, by an analysis of variance that there is no significant difference between patients in their responses to the various drugs tested (24). The potency of other drugs can be estimated by the same procedure (Figure 12).

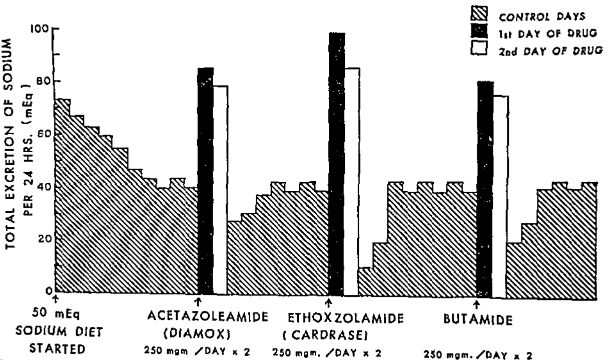


Figure 12. The technique for determining potency of diuretics based on changes in sodium excretion. Increased sodium excretion is followed by 1 to 3 days of retention before equilibrium is again established

Chapter 4

THE PHARMACOLOGY AND CLINICAL USE OF THE MERCURIAL DIURETICS

Of the different types of diuretic compounds employed today, the mercurials are the most powerful and consistently dependable. They have, to a considerable extent, superceded the less reliable xanthine diuretics, especially in the more severe cases of congestive heart failure. While digitalis still remains the most useful agent for improving cardiac function in cardiac decompensation, digitalis alone sometimes fails to completely eliminate the edema. The use of mercurial diuretics has materially improved the management and well-being of these patients. These two types of drugs, of course, act by entirely different mechanisms and each tends to complement the action of the other

The Chemistry of Mercurial Diuretics. The mercurial diuretics in current use are organomercurial compounds that have been reacted with theophylline, thioglycollic acid or some other group The early mercurial diuretics were compounds of the general type RHgOH. Compounds in current use are produced by the following reactions:

1 $RHgOH + H(C_7H_7O_2N_4) = RHg - (C_7H_7O_2N_4) + H_2O$
(theophylline)

2. $RHgOH + HSCH_2COOH = RHg - S\ C\ H_2C\ O\ O\ H + H_2O$
(thioglycollic acid)

3. $RHgAC + NaCl = RHg - Cl + NaAc$

The organomercurials formed by the above reactions confer upon each type of compound unique properties not directly related to the parent compound or to each other. Because of the special properties of each of these agents, they have different therapeutic applications

Mechanism of Action. In the years immediately following Vogel's (106) discovery of diuretics produced by an organic mercurial compound, much fruitless labor was devoted to studies attempting to prove an extrarenal mechanism of action. Many of the techniques employed during this period for such studies were faulty and subsequent work has *overwhelmingly favored a direct renal effect as the* primary mechanism of action.

As early as 1928, Govaerts (39) provided unequivocal evidence that diuresis from a mercurial diuretic could be produced by a direct effect on the kidney. He administered an organomercurial diuretic to a dog and at the time of maximal diuresis, transplanted a kidney to a recipient dog. The donor kidney continued to diurese, while the recipient animal's kidneys continued to secrete urine at the control rate. Additional evidence of the same nature was obtained by injecting a small amount of a mercurial diuretic into one renal artery of a dog. The injected kidney showed diuresis, but the urine output of the other side remained constant (3). In this experiment, the injected kidney retained most of the diuretic. If larger amounts of the agent are injected into a renal artery, a sufficient amount enters the systemic circulation to produce diuresis on the opposite side also

Renal Functions. A substantial number of studies have been directed toward observations of the effect of mercurial diuretics on renal functions No consistent

TABLE VI

THE DIURETIC ACTION OF MERALLURIDE AND ITS EFFECTS ON RENAL FUNCTIONS Study performed on a 13-kg dog Note that vasopressin did not suppress meralluride diuresis (After Handley (42), courtesy *Pharmacology in Medicine* V.A. Drill, Ed, Blakiston Div, McGraw Hill Book Company, 1954)

Time min	*Urine Volume, cc Per Min*	*Glomerular Filtration Rate, cc Per Min*	*Renal Plasma Flow, cc Per Min*	*Sodium Excretion, μEq. Per Min*
		CONTROL		
0-10	0 55	45	215	12
10 20	0.50	43	220	17
21		Meralluride, 0 1 cc per kg, I V		
31 41	3 00	39	203	130
41 51	5.20	35	211	180
51-61	7.50	34	214	360
62		Vasopressin, 5 units, I.V		
62 72	11 00	35	201	1050

change has been observed to occur, except for a depression of the renal tubular reabsorption of sodium chloride and water. This is true of normal or edematous subjects and experimental animals. Thus, the glomerular filtration rate may rise, fall or show no change. Changes in renal plasma flow show a similar inconsistency (Table VI). One must conclude from these observations that changes in glomerular filtration rate or renal plasma flow are not involved in the diuretic effect of these agents.

Tubular Inhibition. Considerable effort has been devoted to the problem of the site and mechanism of mercurial inhibition of electrolyte and water reabsorption by the renal tubules. It is generally assumed, from indirect evidence, that the site of action is limited to the terminal portions of the proximal tubules. Pathological studies have indicated that the nephrotoxic action of mercury is limited to the terminal part of the proximal tubules unless very large doses are used. In the latter instance, entire nephrons, including the collecting ducts, may be damaged These observations may not have any bearing on the site of action of mercurial diuretics because diuresis from these agents is not a nephrotoxic effect. In fact, renal damage from any type of mercury compound usually results in anuria rather than diuresis.

More recently, attempts have been made to localize the site of action histochemically (15,84,90,107). These studies were based on the high affinity of mercurial compounds for protein sulfhydryl groups (-SH) and of the possibility that the sulfhydryl containing enzyme succinic dehydrogenase may be involved in mercurial diuresis (45). The reports of the above workers are conflicting, possibly because unphysiological amounts of mercurial diuretics were used in some of the experiments. In the absence of

unequivocal evidence, the site of action may tentatively be placed in the proximal tubule where active reabsorption of sodium chloride is presumed to occur. In favor of this part of the nephron being the site of action of mercurials is the fact that other functions, presumably located in this segment, are known to be depressed by these agents. The secretion of para-aminohippurate and the reabsorption of potassium and glucose (5,11,83,111) have been observed to be partially inhibited during mercurial diuresis.

The strong affinity of organic mercurial compounds for sulfhydryl groups of protein and other compounds containing -SH groups is well-established (2). Although organomercurial compounds are capable of reacting with carboxyl and amino groups of proteins they first react stoichiometrically with -SH groups to form mercaptides

Dimercaprol (Bal) is a compound containing two -SH groups. The administration of this agent (Figure 13, A.B) promptly suppresses mercurial diuresis (23,44). This inhibitory effect of dimercaprol suggested that it removes the mercurial diuretic from its combination with an -SH containing enzyme due to the formation of a more stable complex. It is well known that certain enzymes require free sulfhydryl groups within the protein structure for activity. Oxidation of the -SH groups to -S-S- or the combination of the -SH groups with a reactive compound produces inhibition. It should not be inferred from the above discussion that the transport system inhibited by mercurial diuretics has been established

Mercurial diuresis has been considered to be due to "a mild and reversible toxic mercury nephrosis without any microscopically visible changes" (106). It should be stated emphatically that such a concept has no basis in fact

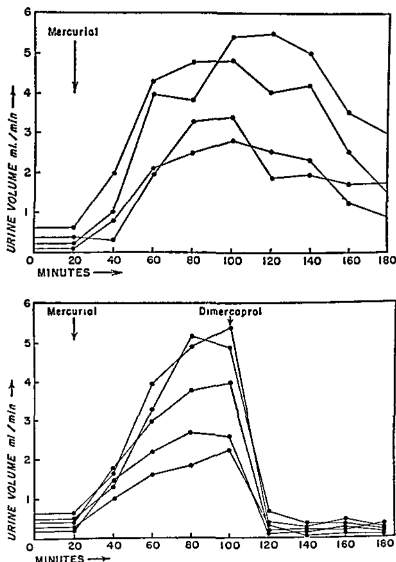


Figure 13A Diuresis curves obtained in dogs from 0 1 cc per kgm of meralluride. B Inhibition of mercurial diuresis by dimercaprol. (After Handley and LaForge (44), courtesy *Pharmacology in Medicine*. V.A. Drill, Ed, Blakiston Div, McGraw-Hill Book Company, 1958)

and is undoubtedly incorrect. Considerable evidence indicates that a reversible inhibition of the mechanism for the active reabsorption of sodium chloride is involved. The inhibitory effect is transient and incomplete.

Electrolyte and water excretion. Undoubtedly, the most important therapeutic effect of the mercurial diuretics is a partial inhibition of the rate of sodium and chloride reabsorption by the renal tubules. It is generally assumed that specific transport systems are present in the cells of the renal tubule for the reabsorption and secretion of different ions and compounds present in the glomerular filtrate and the blood. The composition of the urine before and during mercurial diuresis indicates a highly selective action on only a few of these transport mechanisms. Among the urinary electrolytes, the reabsorption of sodium and chloride are blocked to the greatest extent. There are proponents of the view that the primary effect is on chloride reabsorption and those that favor a primary effect on sodium. While it is true that there is frequently a greater relative increase in the rate of chloride excretion, this may indicate an increased rate of excretion of cations other than sodium Which ion is primarily affected, or whether the absorption of both is inhibited, must for the present be considered undetermined.

The effect of mercurial diuresis on potassium excretion is variable. It is either increased, decreased, or is not changed Mercurials depress the renal tubular secretory mechanism for potassium (4). No serious disturbance of potassium metabolism occurs in the ususal clinical use of these agents *However, if ammonium chloride is* used concomitantly with a mercurial, or if dietary sodium is retained during diuretic therapy, the loss of potassium

may be appreciable. This may account for such symptoms as muscular weakness, nausea and ventricular premature contractions.

Calcium excretion may be moderately increased by mercurials. The excretion of phosphate, sulfate, am-

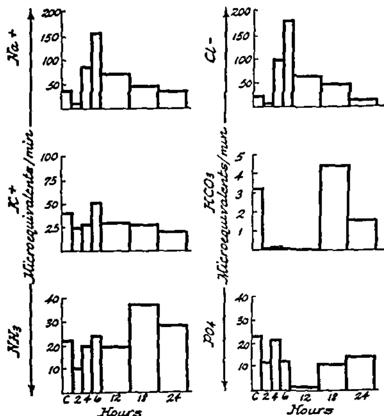


Figure 14. Patterns of electrolyte excretion following the intramuscular administration of one cc of meralluride to a cardiac patient (After Ford, Rochelle, Handley, Moyer and Spurr (31), courtesy *JAMA*.)

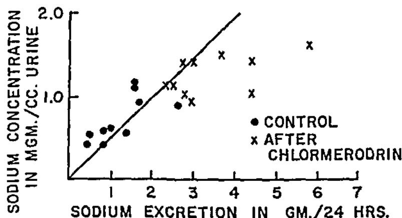
monia hydrogen ions or titrable acidity are not influenced during the period of maximal diuresis and natriuresis. The mercurials do not produce a predictable effect on urinary pH.

During mercurial diuresis, a greater increase in the rate of excretion of sodium chloride than water usually occurs (Figure 15 A,B). This is reflected in an increase in concentration of sodium per unit volume of urine formed. In contrast to the action of these diuretics, when cardiac failure is controlled with digitalis alone, sodium and chloride are lost in the urine in the same concentration as they are present in the extracellular fluid (61,93).

No specific effect of mercurial diuretics or tubular reabsorption of water has been demonstrated. Increased rates of sodium and chloride excretion, usually but not always, precede water diuresis (87). The rate of excretion of these two ions increases five or six fold in the average cardiac patient, whereas urine volume may only increase two or three fold (73).

The sodium chloride and water loss during mercurial diuresis can be accounted for as originating entirely from the extracellular fluid. The fall in plasma potassium, however, is by no means great enough to account for the potassium loss as coming from extracellular fluid alone. Actually, the potassium loss during diuresis is sometimes greater than the total calculated amount of extracellular potassium. Intracellular loss of potassium undoubtedly occurs.

Absorption. The reaction of theophylline with an organic mercurial results in a more stable, less toxic and more rapidly absorbed compound (18). After intramuscular administration of compounds of this type, absorption is



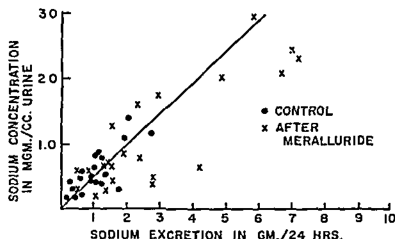


Figure 15A. Increased sodium excretion as well as increased concentration of sodium per cc of urine after intramuscular administration of 40 mgm of Hg equivalent of chlormerodrin (Neohydrin). B. Similar effects from the same dose of meralluride (Mercuhydrin). (After Moyer, Handley and Seibert (72), courtesy *Am. Heart J*)

virtually complete within an hour. The amount of theophylline present in a therapeutic dose of a mercurial is too small (96 mgm) to exert any diuretic effect except by improving the rate of absorption of the mercurial. Organomercurial theophylline compounds in current use include:

Meralluride sodium, U.S.P. (Mercuhydrin sodium)
Mercumatilin sodium, N.N.D. (Cumertilin sodium)
Mercurophylline sodium, U.S.P. (Mercuzanthin sodium)
Merethoxylline, N.N.D. (Dicurin)
Mersalyl and Theophylline, U.S.P. (Salyrgan-theophylline)

A different type of compound has more recently been introduced. In this compound, the theophylline of mercurophylline sodium has been replaced by sodium thioglycollate (56). The mercurial was studied after the ob-

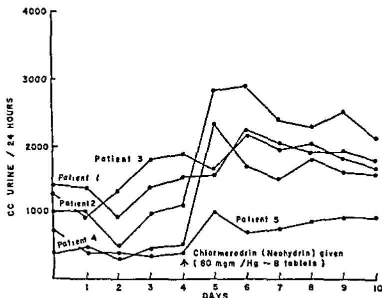


Figure 16 Sodium excretion following the oral administration of chlormerodrin (Neohydrin). (After Moyer, Handley, Seibert and Snyder (73), courtesy *AMA Arch Int Med*)

servations indicated that glutathione and cysteine reduce the cardiac toxicity of mercurials without influencing the diuretic effect. The compound is known as mercaptomerin sodium (Thiomerin sodium). After intramuscular injection the rate of absorption of mercaptomerin is of the same order as the compounds mentioned above.

Before the development of the theophyllinated derivatives of the organomercurial compounds, the intravenous route was preferred because of pain and tissue damage when injected intramuscularly. The intramuscular

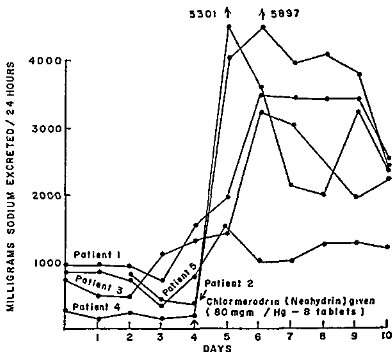


Figure 17. Urine excretion following the oral administration of chlormerodrin (Neohydrin). (After Moyer, Handley, Seibert and Snyder (73), courtesy *AMA Arch. Int Med*)

route is now commonly employed. Rapid and complete absorption occurs with minimal pain in most patients. Intravenous administration is not without danger because of the potential hazard of cardiac toxicity. Mercaptomerin is an exception in that it has low cardiac toxicity. Any of these agents given intravenously should be injected slowly and preferably should be well diluted.

With the advent of mercaptomerin (Thiomerin), subcutaneous injection has had its advocates. Meralluride and mercaptomerin have both been extensively and successfully used by this route.

The rate of excretion of mercury after subcutaneous, intramuscular, and intravenous administration of meralluride is quite similar. This indicates that the rates of absorption are rapid from both subcutaneous and intramuscular sites (see Figures 18 and 19).

Oral therapy has been unsatisfactory until the recent introduction of chlormerodrin (Neohydrin) since absorption of most mercurial diuretics from the intestinal tract is limited. After oral administration of compounds other than chlormerodrin the amount of mercury that may be recovered from the urine is less than 3 per cent of the dose administered. This necessitates the use of large doses that frequently cause gastrointestinal distress. A significant advance in oral therapy was made with the development of chlormerodrin. Not only is this compound better absorbed from the intestinal tract (up to 12 per cent), but it is several times more potent than other mercurials currently employed (43) These two properties of this agent make effective oral diuretic therapy (Figures 16 and 17) possible without a high incidence of untoward reactions (75).

The use of mercurial diuretics in the form of rectal

TABLE VII

THE EFFECT OF SEVERAL MERCURIALS ON WATER AND ELECTROLYTE EXCRETION IN CONGESTIVE HEART FAILURE. Male, aged forty-three, with congestive failure. Daily sodium and water intake were 2,300 mg and 4,000 cc. respectively. Meralluride was given intramuscularly, mercaptomerin subcutaneously, and Chlormerodrin (Neohydrin) orally. Several days with no medication were allowed to elapse before succeeding drug was administered. (After Ford and Moyer (26), courtesy *Pharmacology in Medicine*, V.A. Drill, Ed., Blakiston Div., McGraw-Hill Book Company, 1954.)

	Dose, mgm Hg	*Weight, kgm.*	*Urine Volume cc per 24 hrs*	*Chloride Excretion, mEq/24 hrs.*	*Sodium Excretion, mEq/24 hrs*
Control		77	2,930	25	50
Meralluride	39	77	4,700	167	315
Meralluride	39	76	3,200	16	41
Control		75.8	2,900	19	39
Mercaptomerin	40	73.8	3,720	12	51
Mercaptomerin	40	76.2	4,730	226	402
Control		72.8	3,360	55	73
Chlormerodrin	40	72.8	4,640	200	340
Chlormerodrin	40	70.4	3,250	45	85
Control		72.4	3,250	80	101
Meralluride	78	73.0	5,500	422	557
Meralluride	78	70.4	2,480	14	41
Control		72.6	2,740	41	65
Mercaptomerin	80	73.0	5,580	440	575
Mercaptomerin	80	71.4	3,020	58	41

suppositories has never been a popular form of therapy. Poor absorption and local irritation are largely responsible for the opposition to the use of this route. Some agents, such as mersalyl (Salyrgan), cannot be used in suppositories because of the danger of ulcer formation. This form of therapy has, however, proven to be effective in some patients with cardiac edema.

Fate. After absorption or intravenous injection, mercurial diuretics are probably largely transported as complexes with the single sulfhydryl group of mercaptalbumin. One mercuric ion has been demonstrated to react with two albumin molecules (51). Although it has not been proven, it seems likely that the theophylline moiety of mercurials is split off after absorption, thus making it possible for one mole of the mercurial to react with one mole of mercaptalbumin. It is also possible that the organomercurial radical combines with other substances in the plasma containing sulfhydryl groups

It has been inferred that the distribution of mercurial diuretics in the various tissues of the body follows a pattern similar to that found with inorganic mercury. Undoubtedly, this is a falacious assumption After inorganic mercury administration, the metal may be found widely distributed throughout most of the tissues of the body (103). The mercurial diuretics on the other hand, are much more rapidly excreted and no appreciable amount of mercury can be found in any of the tissues except the liver, kidneys and spleen in animals during prolonged administration of diuretics (48). Following intravenous administration of a mercurial diuretic, the compound rapidly leaves the plasma, probably due to removal by the liver and kidneys. During the early phase of the diuretic period, the liver contains the largest ab-

TABLE VIII

Mercury Excretion in Urine and Feces Following Oral Administration of Chlormerodrin (Neohydrin) in a Single Dose Containing 60 mgm Hg (After Moyer, Handley, Seibert and Snyder (73) courtesy American Medical Association *Archives of Internal Medicine*)

Dog No.	*Mercury in Urine, mgm*						*Mercury in Feces, mgm.*							
	Time After Ingestion, Hr				*Total "Absorbed"**		*Time After Ingestion, Hr.*						*Total Hg Recovered†*	
	24	48	72	96	Mg	%	24	48	72	96	120	144	Mg	%
1	3.60	0.52	0.00	0.00	4.12	7	44.00	1.65	0.15	0.04	0.00	0.00	49.96	83
2	4.33	1.20	0.20	0.14	5.85	10	4.50	41.22	3.42	2.00	0.66	0.34	57.99	97
3	2.24	0.10	0.14	0.00	2.48	4	12.92	24.20	0.71	0.20	0.07	0.02	40.60	68
4	4.93	0.76	0.10	0.00	5.97	10	40.25	2.03	1.12	0.21	0.00	0.00	49.40	82
5	2.88	0.51	0.25	0.00	3.64	6	38.21	10.00	2.13	0.30	0.00	0.00	54.28	90
6	1.78	1.34	0.00	0.00	3.12	5	34.20	0.00	5.00	—	0.48	0.00	42.80	71
7	1.35	3.22	0.23	0.00	4.80	8	45.10	4.91	0.89	0.51	0.32	0.02	56.55	94
8	2.60	1.23	0.00	0.00	3.83	6	35.11	7.80	0.41	0.15	0.11	0.00	47.41	79
9	2.10	0.38	0.11	0.00	2.59	4	312.00	10.25	0.34	0.08	0.03	0.00	44.49	74
10	4.32	0.13	0.03	0.00	4.48	7	41.30	2.64	0.26	0.15	0.05	0.00	48.88	81
Mean	3.01	0.94	0.12	0.01	20.7	7	32.68	10.47	1.44	0.40	0.17	0.04	49.24	82

* Previous observations indicate that 90% of diuretic administered intravenously is excreted in the urine.
† Total recovered in urine and feces expressed in per cent of amount ingested

solute amount of the compound of any tissue or organ but the kidneys contain the highest concentration per gram of tissue (48).

Excretion. A considerable percentage of administered mercurials *appears in the urine before diuresis begins.* This is probably a reflection of the time required for a critical amount of the compound to react with and to inhibit the transport mechanism of the renal tubules responsible for the reabsorption of sodium chloride. In the meantime, a considerable amount of the compound escapes this reaction and appears in the urine.

In cardiac patients about 30 per cent of a therapeutic *dose of a mercurial, given parenterally, is excreted in 3* hours. The largest amount is recovered after 6 hours and there is an abrupt drop in the excretory rate during the following 6 hour period. When no renal impairment is present, up to 90 per cent may be recovered in the *urine in 24 hours (Figure 18).*

In normal subjects, there is little difference in the rate of excretion when the mercurial is administered by *the different parenteral routes Excretion after subcu*taneous and intramuscular administration may be somewhat slower in cardiac patients with edema, but excretion rates when injected intravenously may approach that seen in normal subjects (Figure 19). Fecal excretion of mercury seldom exceeds 5 per cent of the administered dose when given parenterally. The diuretic enters the intestinal tract with bile, although a small amount is probably excreted directly by the intestinal mucosa. With oral mercurial therapy, most of the diuretic remains unabsorbed and is eliminated in the feces. As used therapeutically for the treatment of edema, there is no evi-

dence to indicate that these compounds accumulate in the body.

In spite of many statements to the contrary, there is no evidence for the concept that the diuretic action of the organomercurials is due to the release of inorganic mercury. Polarographic studies have demonstrated mercurial diuretics are excreted as an organic compound, probably as a cysteine complex (109). A method has been devised, utilizing adsorption chromatography, for separating the urinary excretory products of meralluride (49). The method is based on the capacity of aluminum oxide to adsorb carboxylic acid compounds Since meralluride is the sodium salt of a carboxylic acid, it is firmly bound to the adsorbent, while noncarboxylic mercurial and inorganic mercury is readily washed through the adsorbent column with distilled water. The application of this method to urines collected during mercurial diuresis

TABLE IX

TISSUE CONTENT OF MERCURY SEVEN DAYS AFTER INGESTION OF SIX TABLETS OF (60 mgm of Hg) CHLORMERODRIN (NEOHYDRIN) (After Moyer, Handley, Seibert, and Snyder (73), courtesy of the American Medical Association *Archives of Internal Medicine*)

Dog No	Total Hg, mgm Heart	Liver	Kidneys
1	0 00	0 36	0 61
2	0 00	1 93	0 36
3	0 02	0 19	0 44
4	0 00	0 60	0 00
5	0 00	0 34	0 36
6	0 06	1 35	0 88
7	0 02	1 15	0 38
8	0 00	0 48	0.21
9	0 03	1 02	0 68
10	0 00	0 92	0 43
Mean	0 01	0 83	0 44

results in the separation of two fractions containing mercury. The fraction adsorbed is always, by far, the larger of the two and probably represents unchanged meralluride or the compound in combination with cysteine. Diuresis is proportional to the rate of excretion of this fraction. The compound containing mercury that is not adsorbed has not been identified. It may be decarboxylated meralluride. This fraction represents about 5 per cent of the total mercury administered and is not related to the diuretic effect.

Potentiation. Mild acidosis such as may be produced by ammonium chloride enhances the diuretic response from mercurials. This is actually a synergistic effect. Alkalosis tends to inhibit the diuretic action of these compounds. The mechanism by which alterations in the acid-base bal-

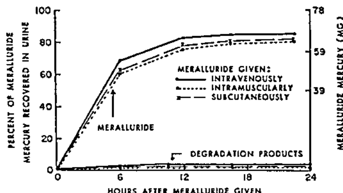


Figure 18 Comparison of rates of excretion of meralluride mercury and non-meralluride mercury when given by three different routes to normal subjects (average values from four subjects given the diuretic by each route) (After Moyer, Handley and Seibert (74), courtesy *Ann. N Y Acad Sci*)

ance alter the response to diuretics is unknown. The potency of mercurial diuretics is sufficiently great that ammonium chloride need not be given with the mercurials except when hypochloremic alkalosis develops.

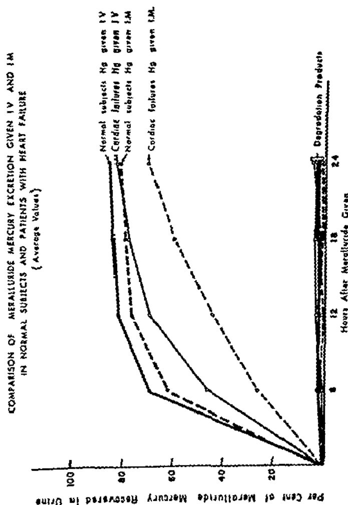


Figure 19. Comparison of meralluride mercury excretion after intravenous and intramuscular administration in normal subjects and patients with heart failure. (After Moyer, Handley and Seibert (74), courtesy *Ann. N. Y. Acad. Sci*)

Clinical observations on potency and therapeutic use of mercurial diuretics. Although the organomercurial compounds have been used primarily for the treatment of patients with moderately severe and severe heart failure, they are also effective for promoting diuresis in most conditions in which water and salt retention is a problem. Clinical potency of the organomercurial compounds varies greatly. Whether using orally or parenterally administered mercurials, it is essential that adequate dosage be employed. For example, in Figure 21 a study is summarized in which a group of patients with congestive heart failure was treated with an inadequate dose (equivalent to 20 mgm

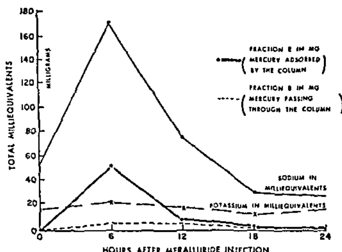


Figure 20 Relation of rate of excretion of meralluride and nonmeralluride mercury to that of sodium and potassium in cardiac patients after 2 cc of meralluride intravenously (After Moyer, Seibert and Handley (81), courtesy *Circ Research*)

Hg) of chlormerodrin (65). The therapeutic failure rate was 76 per cent. When these same patients were later given an adequate dose (equivalent to 80 mgm Hg) of the drug, the therapeutic failure rate was reduced to only 9 per cent Interpretation of these results after administration of the smaller dose would have prompted the conclusion that the drug was no better than a placebo, when actually an inadequate dose was used.

A determination of the threshold dose and the approximate maximum tolerated dose for each drug is essential. Although potency estimations and threshold dosage of each drug have been determined, all patients are not equally responsive. Consequently, the dosage of each drug which is adequate but yet not excessive must be determined for each individual patient when long term, continuous therapy is employed.

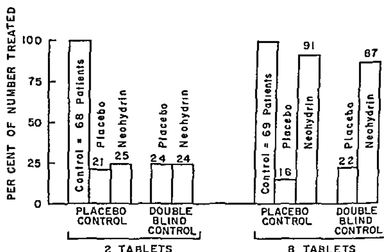


Figure 21. Comparison of clinical control of heart failure in patients receiving inadequate followed by adequate doses of Neohydrin. (After Moyer (65), courtesy *AMA Arch. Int. Med*)

The dosage response curve, based upon weight loss as an estimate of diuretic potency, which was obtained for meralluride (mercuhydrin), shows logarithmic progression between the 0.5 and 2 cc (equivalent to 20 to 80 mgm Hg) doses. Increasing the dose above this level has very little additional diuretic effect (79). By comparison, the dosage response curve obtained for diglucomethoxane (mersoben) administration indicates that the diuretic effect is still increasing progressively at the 2 cc dose (equivalent to 80 mgm Hg). Diglucomethoxane and meralluride follow a similar and parallel dosage response curve but diglucomethoxane appears to be more potent than meralluride (Figure 22) both in the smaller doses and the larger doses. A dose of diglucomethoxane equivalent to 20 mgm Hg (0.5 cc) appears to be approximately equivalent to a dose of meralluride containing 30 to 40 mgm Hg (0.8 to 1 cc) In this dosage range both are equivalent to a dose of acetazoleamide (Diamox) of 500 mgm. It is significant that with increasing doses of the organomercurials, there is an increasing diuretic effect, although limited. Contrariwise, the diuretic response to acetazoleamide is no greater at the 2000 mgm

TABLE X

COMPARATIVE POTENCY OF VARIOUS ORGANO-MERCURIAL DIURETICS (After Moyer, Ford, Handley and Spurr (67), courtesy AM & CT)

Diuretic	*Route of Administration*	*Potency Estimation*
Meralluride (Mercuhydrin)	Intramuscular	1 0
Diglucomethoxane (Mersoben)	Intramuscular	1 3
Mercaptomerin (Thiomerin)	Intramuscular	0.6
Chlormerodrin (Neohydrin)	Oral	0.5

dose than it is at a dose of 250 mgm. These observations suggest that a significant indication for diglucomethoxane would be in the patient with severe heart failure who requires a diuretic of greater potency than is available at maximum doses of mercaptomerin and possibly meralluride.

When diglucomethoxane given parenterally is compared with chlormerodrin (Neohydrin) given orally, parallel (Fig. 23) curves are not obtained but both show linear responses. Diglucomethoxane is effective at a much smaller dose (mercury equivalent) than chlormerodrin. This is due to the different methods of administration and incomplete absorption of chlormerodrin from

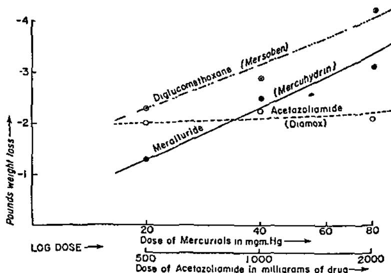


Figure 22. Dosage-response curves comparing two parenterally administered mercurial diuretics (Mersoben and Mercuhydrin) with an orally administered carbonic anhydrase inhibitor (Diamox). (After Moyer, McConn, Seibert, Dennis and Hughes (79), courtesy *J. Chronic Dis.*)

the intestinal tract. As a result, it is necessary to administer a relatively large amount of chlormerodrin before an adequate amount is absorbed and delivered to the kidneys to reach the diuretic threshold in the renal tubules. However, as the diuretic threshold to chlormerodrin is exceeded, the dosage response curve rises very rapidly. The diuretic response to lcc of diglucomethoxane (equivalent to 40 mgm Hg) given parenterally and 8 tablets (equivalent to 80 mgm Hg) of chlormerodrin given orally will approximate each other.

Chlormerodrin, the most widely used oral preparation of the organomercurials, has been shown to be very effective in controlling mild to moderately severe heart failure and fairly effective in severe heart failure. Oral mercumatilin is less effective than chlormerodrin.

A significant advantage to orally administered organomercurials, in contrast to carbonic anhydrase inhibi-

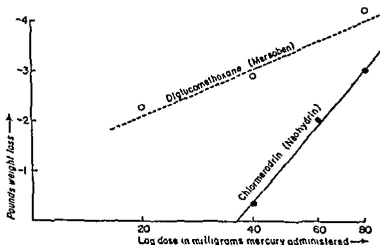


Figure 23. Dosage response curves comparing parenterally administered Mersoben with orally administered Neohydrin. (After Moyer, McConn, Seibert, Dennis and Hughes (79), courtesy *J Chronic Dis*)

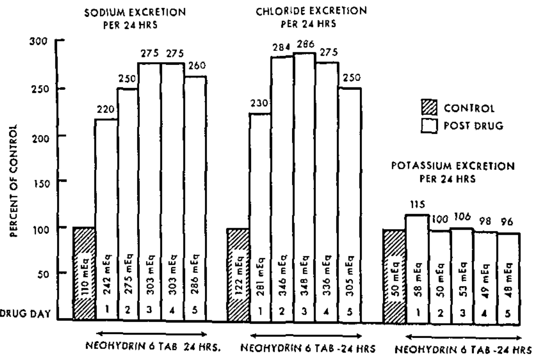


Figure 24A Increased sodium excretion is maintained with daily administration of Neohydrin. (After Ford and Moyer (25), courtesy G/P.)

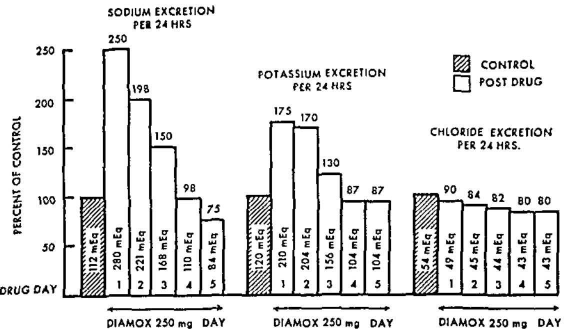


Figure 24B Compensation develops after the administration of a carbonic anhydrase inhibitor for a few days (After Ford and Moyer (25), courtesy *G/P*)

tors, is that the former continue to produce diuresis and natriuresis with continued daily administration (Fig. 24A). With the latter drugs, *tolerance* develops within 2 or 3 days so (Figure 24B) that an interrupted program of drug administration becomes necessary. Thus, when continuous daily diuresis is mandatory, carbonic anhydrase inhibitors are inadequate. This immediately relegates these agents to the therapy of mild heart failure and the treatment of states of sodium and water retention in which sodium and water retention is not a serious problem.

The sodium and water retention associated with steroid administration is one of the more difficult problems to treat. Here orally administered organomercurials seem to be particularly effective. In our experience, persistent low grade diuresis is more effective than massive intermittent diuresis as is obtained following intramuscular administration. To be sure, when the drug is given parenterally, the initial response is more marked, but within 12 hours, this effect is lost and secondary retention of sodium and water occurs (Figure 25). Consequently, the net loss by giving the diuretic every 48 hours is frequently nil. The marked secondary retention of sodium and water is usually not seen in the patient with edema due to heart failure. When parenterally administered mercurial diuretics are to be employed in treating patients for sodium and water retention due to steroid administration, they should be given frequently i.e., every 24 hours or better still, every 12 hours. This same effect can be obtained more conveniently by employing oral mercurials such as chlormerodrin given four times a day, i.e., after meals and at bedtime.

Maintenance therapy with mercurials for patients in heart failure requires careful dose adjustment and gen-

erally speaking, frequent small doses are superior to large but infrequent doses. This is the big advantage of orally administered mercurials which are given daily. The use of an oral mercurial diuretic daily avoids massive edema formation and avoids complications that occur when the markedly edematous patient is subjected to rapid diuresis. Slow, regular diuresis is less apt to produce abnormalities in body fluids and electrolytes. The less serious but often annoying muscle cramps that follow the administration of parenteral mercurial diuretics are also avoided by oral therapy. Treatment is inadequate if the patient is given diuretics only intermittently, after the retention of large amounts of fluid. It is always desirable to keep the patient compensated and free of edema at all times. When a patient loses 5 pounds weight or

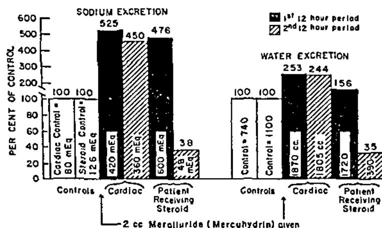
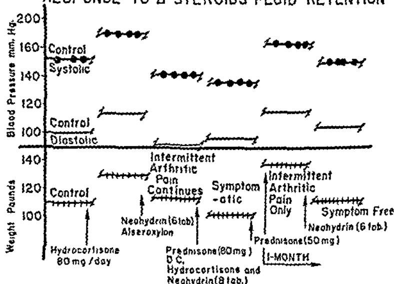


Figure 25 Comparison of the diuretic response to meralluride with edema caused by steroid administration with that of a patient with congestive heart failure. (After Spurr, Curd, and Moyer (99), courtesy *G/P*.)



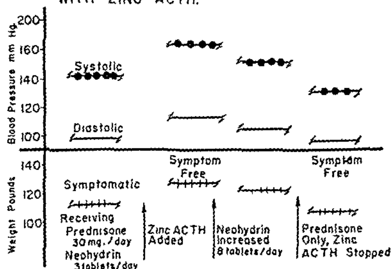


Figure 26 A, B. The control of steroid edema by the daily administration of Neohydrin. (After Spurr, Curd and Moyer (99), courtesy G/P.)

more at each dose the drug should be given more frequently to maintain a more constant weight.

Albuminuria and an elevated blood urea nitrogen are frequently found in patients with heart failure and are not necessarily an indication of primary renal disease. Therefore, these findings do not in themselves contraindicate mercurial diuretics.

Side Reactions in the Choice of a Mercurial Diuretic. The side effects of mercurial diuretics may be considered under three main headings. (1) mercurialism; (2) hypersensitivity; and (3) excessive diuresis, i.e., (a) electrolyte depletion, and (b) vascular complications. The problem of toxicity to mercurial diuretics has been adequately described earlier in this chapter. Therefore, only problems which need emphasis will be reviewed here.

Cardiovascular toxicity of mercurials is frequently mentioned by clinicians but is not a serious problem. There have been no deaths due to cardiovascular collapse following the intramuscular, subcutaneous, or oral administration of currently available organomercurial diuretics. Kaufman (54) in a review of the literature for a 23-year period found reports on 32 such fatal cases, all following intravenous administration of the drug Therefore, the intravenous route should be avoided when possible. When necessary to give the drug intravenously, it should be given slowly over a period of 5 to 10 minutes. It is probably best to give the drug in 200 cc. of 5 per cent glucose as a slow intravenous infusion over a 20 to 30 minute period. The intravenous route of drug administration may become mandatory because of the absorption problem when massive anascara is present.

Gastrointestinal symptoms may follow mercurial administration by any route especially when large doses are

TABLE XI

COMPARISON OF THE SIDE EFFECTS OF DIURETICS

	Acetazoleamide (Diamox)		*Chlormerodrin (Neohydrin)*		*Meralluride (Mercuhydrin)*		*Mercaptomerin (Thiomerin)*	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Number of patients treated	18	100	18	100	50	100	75	100
Side effect								
Diarrhea	0	0	4	22	—	—	—	—
Gastro intestinal cramps	0	0	5	28	3	6	4	5
Nausea	1	6	5	28	5	10	7	9
Vomiting	0	0	0	0			—	—
Weakness	3	17	4	22			—	—
Anorexia	2	11	4	22			—	—
Pain at injection site	—	—	—		10	20	8	11
Leg cramps	—	—	—	—	13	26	16	21
Rash	—	—	—		3	6	3	4
Fever	—	—	—	—	—	—	2	3
Uticaria		—	—	—	1	2	4	5
Malaise	—		—	—	12	24	16	21
Confusion	—	—	—	—	1	2	—	—
Urinary retention	—	—	—	—	1	2	—	—

employed. However, these symptoms are rare following parenteral administration and frequent following oral administration due to the local irritant effect of the drugs (Table XI). Nausea and vomiting are observed after parenteral administration only when the dose is in excess of 160 mgm Hg equivalent. The cause of this reaction is not known to the authors.

In a growing list of organomercurials for oral use, chlormerodrin is the most effective agent which is currently available. Oral chlormerodrin has less than a 25 per cent toxicity index, and has a potency estimation of 0.5, i.e., it is half as effective as parenterally administered meralluride, making it ideal for maintenance of the edema free state. The oral organomercurial, Cumertilin, was found to have a toxicity index of more than 25 per cent and produces less than 100 per cent increase in sodium excretion under controlled conditions. Meralluride given parenterally has a toxicity index of 15 per cent and has a designated potency estimation of 1. It is the most potent organomercurial commercially available for parenteral use, and may be used in the treatment of severe edema.

Pain at the site of injection is a variable response. There is little doubt that mercaptomerin produces less pain at the site of injection when given subcutaneously than other currently available preparations. However, following intramuscular injection this difference in pain response is less in evidence.

Dermatological reactions are usually signs of sensitization. The rash frequently starts with pruritis and may develop into urticaria. This may progress to a morbilliform or purpuric rash which, and if the drug is continued, to exfoliative dermatitis. When a skin rash appears the drug should be discontinued immediately. Frequently,

another mercurial diuretic may be substituted without producing a skin reaction. This suggests that the sensitization phenomena is a response to the structural configuration rather than a response to the mercury.

There is no evidence to indicate that organomercurial diuretics are nephrotoxic (40,55). Leff and Nussbaum have followed patients who have received chlormerodrin daily for a period of 4 years without producing renal damage (55). Some of these same patients had previously received meralluride parenterally for periods up to 6 years. However, in patients with marked oliguria due to primary renal disease, mercurial diuretics not only are ineffective but are probably contraindicated. When oliguria associated with salt and water retention due to other causes is a problem, even in the presence of chronic renal disease, mercurial diuretics may be used with impunity (40).

Some less common side effects associated with mercurial administration are stomatitis, gastritis, and peptic ulcers These are seen most frequently following prolonged oral administration. Stomatitis is found almost exclusively in patients with poor oral hygiene. Gastritis and peptic ulcers are due to the local irritation of the drug. Therefore, oral mercurials should be used with caution in patients with previous ulcer history.

Mercurial resistance and electrolyte abnormalities associated with mercurial therapy. Mercurial fastness is a relative term. Gorden and Greenblatt found that patients who did not respond to meralluride or diglucomethoxane become responsive when larger doses of the drug were given by slow intravenous infusions (38). Even at doses of 3 mgm Hg per kgm of the diuretic, no toxicity was noted. When

the mercurial diuretics are given in this manner, potassium excretion is also increased.

In approaching the refractory patient, one must be certain that some underlying cause of the heart failure is not at fault. Such things as hypermetabolism, peripheral arteriovenous fistula, beri beri, severe anemia, pulmonary disease, Paget's disease, etc., must be ruled out. Finally, one must remember that the patient with heart failure, particularly if due to an inadequate coronary circulation, is never cured. Therapy only makes the altered physiological mechanisms more effective and more able to meet the demands of the individual's circulatory requirements. The disease process is generally a deteriorating condition and finally there comes a time when it is no longer possible to maintain compensation no matter how energetic therapy may be As Harrison has stated rather simply, "The machine just gets old and wears out." Glomerular filtration rate is progressively impaired, as the disease process advances, so that inadequate amounts of sodium and water are filtered to obtain a diuretic response It is in these patients that the intravenous administration of 0.5 to 1 gram of aminophylline, given intravenously one to two hours after the mercurial, will frequently cause diuresis in a previously unresponsive patient. When mercurials are given parenterally to these patients, they are not excreted promptly. Consequently, the molecular structure may be altered and the percentage of degradation products increased (81). Therefore, continued daily administration of large doses should be undertaken with caution

When refractoriness to the mercurial diuretics does develop, an attempt should be made to find causative factors. If they are present, and can be corrected, the patient will again become responsive to therapy. Abnormal

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TABLE XII

DIFFERENTIAL DIAGNOSIS OF TWO ELECTROLYTE ABNORMALITIES AS A COMPLICATION OF MERCURIAL DIURETIC ADMINISTRATION

	Hypochloremic Alkalosis	*Low Salt Syndrome*
Incidence	Common	Relatively uncommon
Prognosis	Fair to good	Grave even with proper treatment
Serum Cl	*Markedly decreased in greater proportion than Na*	Decreased moderately but in lesser proportion than Na
CO_2 combining power	Increased, alkalosis	Decreased, acidosis
Serum Na	*Slight decrease or normal*	Markedly decreased
NPN	No rise early, NPN normal until late	Early azotemia prominent, NPN markedly elevated
Urine Cl	*Normal or increased*	Decreased to absent
Urine pH	Acid range	Alkaline range
Hematocrit	Decreased, hemodilution, hypotonicity	Increased; hemoconcentration, hypertonicity
EKG	K deficiency	No characteristic changes

plasma electrolyte patterns following diuretic therapy is one of the frequent causes of refractoriness. These can usually be corrected by the administration of appropriate electrolytes. Four types of electrolyte imbalance may develop: (1) chronic dilutional hyponatremia, (2) hypochloremic alkalosis, (3) salt depletion syndrome, and (4) potassium deficiency.

Chronic dilutional hyponatremia is one of the most serious metabolic derangements and is apparently unrelated to treatment unless concurrent primary renal disease is present. Under the latter circumstances, if fluids of low sodium content are given in excess of the kidney's ability to excrete water, dilutional hyponatremia results. The syndrome results from extreme dilution of extracellular fluid. Presumably, excessive ADH activity may also

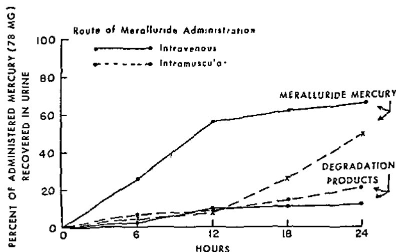


Figure 27. The urinary excretory products from meralluride in a patient unresponsive to mercurial diuretics. Separated by partition chromatography. (After Moyer, Seibert and Handley (81), courtesy *Circ. Research*)

fluid. The plasma sodium concentration is about the same as the extracellular fluid sodium concentration. Therefore, normal plasma sodium (140 mEq per L) minus the measured plasma sodium (milliequivalents) in the patient, multiplied by the extracellular fluid volume (20 per cent x body weight) equals the amount of sodium required (in milliequivalents) to correct the hyponatremia in the extracellular fluid compartment. One cc of 5 per cent sodium chloride equals 0.85 milliequivalents Thus:

$$\frac{\text{Body Wt. (kgm)} \times .20 \times 140 - (\text{patient's plasma sodium in mEq})}{85} = \text{cc of 5 per cent sodium chloride to be administered}$$

This salt solution should be given slowly by intravenous infusion over a period of two hours or more. It is important to restrict fluids (especially water) while the 5 per cent salt is being given and for some time thereafter. Otherwise, the plasma sodium will be diluted again, the blood volume increased, and the heart failure aggravated After 12 hours, for allowing adequate time for equilibrium and stability to occur, the plasma sodium concentration should again be determined. The process must then be repeated if hyponatremia continues. It is an error, in our opinion, to attempt to bring sodium levels entirely to normal. Furthermore, only if the sodium level is below 125 mEq is correction with 5 per cent salt solution indicated; then only if the clinical symptoms demand it (severe oliguria, extreme weakness and lethargy, and cerebral symptoms). Otherwise, a liberalized salt intake will suffice. After the syndrome is corrected, the patient is then treated as a severe cardiac, employing bed rest, digitalis and diuretics as before.

Another complication of diuretic therapy is potassium deficiency. This may precipitate digitalis toxicity. Clin-

cause this syndrome. In the absence of severe primary renal disease in patients with heart failure, the syndrome is indicative of severe myocardial impairment. Serum sodium and chloride are low although total body sodium is excessive. Prognosis is hopeless and replacement therapy is seldom successful.

Hypochloremic alkalosis and salt depletion syndrome occur as a complication of vigorous mercurial therapy and rigid salt restriction. In hypochloremic alkalosis, the main deficit is chloride. In salt depletion syndrome it is sodium. Lassitude, apathy, anorexia, and oliguria are the clinical signs, and mercurial fastness occurs in both conditions. The main differences between the two syndromes are tabulated in Table XII. Hypochloremic alkalosis is ususally indicative of severe myocardial disease. It is difficult to produce this syndrome in normal subjects or in patients with only mild heart failure, even with vigorous daily mercurial diuretic administration.

Therapy of hypochloremic alkalosis is directed at replacement of chloride with oral ammonium chloride. For this purpose, at least 2 grams (30 grains) should be given every four hours. It is best to give the drug after meals in order to avoid nausea and vomiting Hypochloremic alkalosis can easily be avoided if ammonium chloride, in doses of 1 to 2 grams daily, is given concurrently with the administration of mercurial diuretics.

The sodium deficit in patients with hyponatremia may be calculated from the serum sodium values and replacement can be based on such calculations. We prefer to base our calculations on extracellular fluid sodium concentrations and use 5 per cent sodium chloride for replacement purposes. Twenty per cent of body weight (kgm) is the approximate volume of the extracellular

Chapter 5

THE PHARMACOLOGY AND CLINICAL USE OF CARBONIC ANHYDRASE INHIBITORS

EARLY IN THE use of sulfanilamide, it was noted that the drug produced a consistent reduction of plasma bicarbonate. Preceding this effect, the urine was observed to become alkaline as a result of increased bicarbonate excretion. The discovery that sulfanilamide is an inhibitor of carbonic anhydrase and the demonstration of a high concentration of this enzyme in the kidney provided a basis for the mechanism of action of the drug (17, 59) Carbonic anhydrase is a zinc-containing enzyme that catalyzes the reversible reaction:



$$H_2O + CO_2 \rightleftharpoons H_2CO_3$$

These reactions occur in the absence of the enzyme, but the presence of carbonic anhydrase greatly accelerates the rates.

Chemistry. Several compounds have been prepared with several hundred times the activity of sulfanilamide. Among these, acetazoleamide (Diamox) and ethoxzolamide (Cardrase) are the only ones in current use as diuretics. Chemically, acetazoleamide is 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide and ethoxzolamide is 6-ethoxybenzothiazole-2-sulfanilamide. They have the following structural formulae:

ically, extreme muscle weakness, cardiac irregularities and abdominal distention are clues that should lead to the diagnosis. Ingestion of 6 to 8 ounces of orange juice on the day of mercurial injection is usually adequate insurance against this complication. Should the complication occur, oral potassium chloride in dosages of 2 to 5 grams daily is indicated.

NaH_2PO_4. This furnishes additional Na^+ for the exchange process and the exchanged Na^+ is again returned to the blood as $NaHCO_3$. Thirdly, in the absence of both $NaHCO_3$ and Na_2HPO_4 in the tubular fluid, H^+ and Na^+ exchange would be self-limiting because of an unfavorable H^+ gradient between tubular cell and the lumen fluid if it were not for an additional function of tubular cells. The exchange

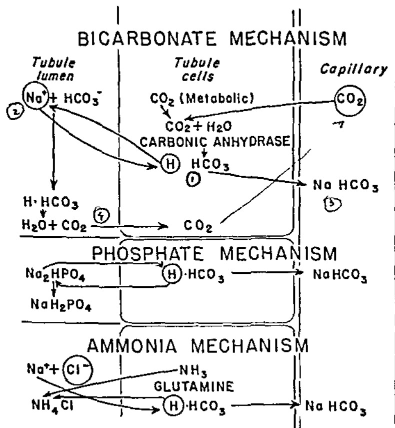


Figure 28 A schematic diagram of the mechanisms for renal base conservation that are inhibited by carbonic anhydrase inhibitors

Acetazoleamide (DIAMOX)

Ethoxzolamide (CARDRASE)

Mechanism of diuresis. The diuretic action of acetazoleamide is intimately related to the mechanisms for maintaining acid-base balance and particularly to the important role of the kidney in this process. Renal mechanisms contributing to acid-base balance are largely concerned with conservation of base and carbonic anhydrase is of prime importance in all these mechanisms. The following renal processes are fundamental for understanding the effects of carbonic anhydrase inhibitors on the kidney (Figure 28). The CO_2 produced metabolically in the cells of the renal tubule is immediately converted to carbonic acid by the enzyme carbonic anhydrase. Urine is acidified by the secretion of H^+ derived from carbonic acid formed in the tubule cells in exchange for Na^+ in the tubule lumen (7). The exchange of these ions normally conserves base in several ways. First, there is virtually complete reabsorption of sodium bicarbonate presented to the tubules in the glomerular filtrate Reabsorbed Na^+ combines with bicarbonate ion in the tubular cells and is returned to the blood. The carbonic acid formed by the reaction of H^+ with bicarbonate ion in the tubular fluid is converted to $H_2O + CO_2$ and the latter is returned to the blood by diffusion. Secondly, even after all bicarbonate is reabsorbed from the tubular fluid, the exchange of H^+ for Na^+ continues to conserve base by other mechanisms. Secreted H^+ converts Na_2HPO_4 from the glomerular filtrate to

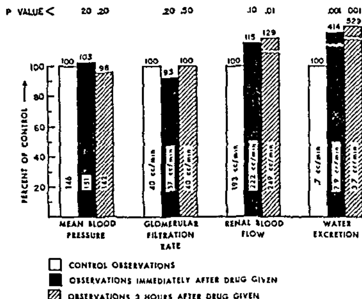


Figure 29. Renal hemodynamic response to acetazoleamide (Diamox) administered in an intravenous dose of 25 mgm/kgm to a dog. (After Moyer and Ford (66), courtesy *Am. J Cardiol.*)

Development of acidosis. The diuretic effect from acetazoleamide is a self-limiting process. With frequent, continued administration of the drug, metabolic acidosis develops and the urinary volume, pH, and various electrolytes approach control levels. Reduction in plasma bicarbonate results in smaller loads being presented to the renal tubules, most of which is reabsorbed so that diuresis no longer can occur Carbonic anhydrase inhibition, however, still continues and therefore, a decreased capacity for H^+ and Na^+ exchange. This makes it impossible for the kidneys to compensate for the abnormal composition of the

of H^+ for Na^+ from NaCl would result in the formation of a strong acid. As the tubular fluid becomes acid, the tubular cells respond by synthesizing NH_3. The ammonia diffuses into the tubular fluid where it immediately reacts with H^+ to form NH_4^+. Ammonia formation thus permits H^+ and Na^+ exchange to continue. These several processes are responsible for returning most of the Na^+ from the glomerular filtrate to the extracellular fluid (4, 89).

The administration of sufficient carbonic anhydrase inhibitor to inhibit renal carbonic anhydrase exerts drastic effects on these base-conserving mechanisms. The decreased rate of carbonic acid formation in the cells of the renal tubules greatly reduces the rate of H^+ and Na^+ exchange. Qualitatively uniform results have been observed in all mammals studied. The urine rapidly becomes alkaline and there is a marked increase in the rate of excretion of sodium, potassium, bicarbonate, and a decrease in excretion of titratable acid and ammonia. With the exception of the increase in potassium excretion, all these changes are explained by the suppression of H^+ and Na^+ exchange. Potassium and H^+ are believed to be secreted by the same mechanism. Therefore, with decreased H^+ formation, the competition of the two ions for the transport mechanism is removed and more potassium is secreted (4).

The stimulus for ammonia formation is an acid urine. With the stimulus removed, ammonia largely disappears from the urine. Increased urine output results from a larger solute excretion, chiefly sodium and potassium bicarbonate. Excretion of chloride is reduced. Excretion of phosphate is not significantly changed. No significant changes in glomerular filtration rate occur, but a slight increase in renal blood flow is frequently seen after these agents. (Figure 29.)

as the changes in weight are recorded following the administration of acetazoleamide (Diamox), ethoxzoleamide (Cardrase), and Butamide. The average increase in the urinary excretion of sodium after the administration of Diamox in a dosage of 250 mgm per day for two consecutive days was 35 milliequivalents per 24 hours. The excretion rate for potassium increased by 35 milliequivalents per 24 hours, while the chloride excretion rate decreased by 9 milliequivalents per 24 hours. The rate of water excretion increased by 0.14 liters per 24 hours, and the weight decreased by 0.3 kilograms per 24 hours. Similar effects were observed after the administration of Cardrase and Butamide.

In contrast to the mercurials, the potency of carbonic anhydrase inhibitors as natriuretic agents is comparatively small (Figure 11). Comparison of the available carbonic anhydrase inhibitors through an analysis of variance reveals no significant difference between any of them in their ability to influence the excretion rates of sodium and other electrolytes as well as water and

TABLE XIII

COMPARISON OF SIDE EFFECTS FOLLOWING ADMINISTRATION OF CARBONIC ANHYDRASE INHIBITORS

SIDE EFFECT	*DIAMOX*		*CARDRASE*		*BUTAMIDE*	
	250 mgm	500 mgm	250 mgm	500 mgm	150 mgm	300 mgm
	Per Cent Incidence					
Diarrhea	—	—	—	46	—	—
G-I Cramps	—	—	—	31	—	22
Nausea	3	6	—	—	—	—
Vomiting	—	—	—	—	—	—
Weakness	6	17	20	62	10	44
Paresthesias	—	6	10	15	10	30
Dizziness	—	—	—	15	—	44
Anorexia	6	11	—	23	—	30

extracellular fluid, so mild acidosis continues as long as the drug is administered. During the period of acidosis, the plasma chloride concentration is high and bicarbonate low.

Comparative Potency. In Table V, the comparative changes in excretion rates of electrolytes and water as well

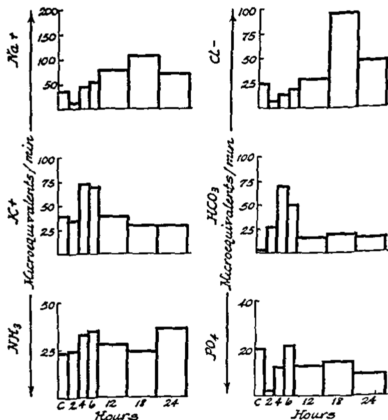


Figure 30. Typical electrolyte excretion patterns after the oral administration of 500 mgm of acetazoleamide to a cardiac patient (After Ford, Rochelle, Handley, Moyer and Spurr (31), courtesy *JAMA*)

chlormerodrin becomes the more effective diuretic when adequate doses are given.

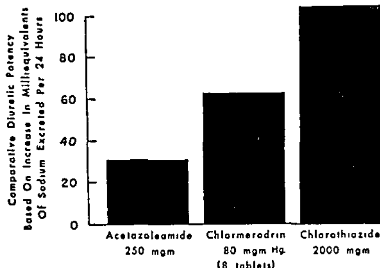


Figure 32. The comparative potency of three oral diuretics as determined by increases in sodium excretion.

Comparison of the effects of an orally administered mercurial diuretic, chlormerodrin (Neohydrin), to acetazoleamide (Diamox) during continued daily administration of each compound reveals other important differences. In Figure 24A it may be seen that the changes resulting from the administration of oral chlormerodrin (Neohydrin) increased with continued administration of the drug. On the first day, the changes due to the carbonic anhydrase inhibitor acetazoleamide was roughly equal to that of Neohydrin, but on continued drug administration there was a continuous decline in response over the five-day period of observation (Figure 24B).

weight changes at the dosages administered. Consequently, one drug of this type has no advantage over another except for the relative incidence and severity of side effects (Table XIII).

At a single dose of 4 tablets (40 mgm Hg equivalent), chlormerodrin is not as potent as acetazoleamide. At a dose of 6 tablets it is equally as potent and doses of 8 tablets or more produce increasingly greater diuresis, when weight loss is used as an index of the diuretic response (Figure 31). Therefore, even in single doses

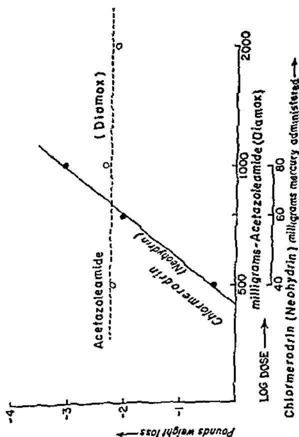


Figure 31. Comparison of the acute response to chlormerodrin to that of acetazoleamide. The response to chlormerodrin increased with the dose but the response to 2000 mgm of acetazoleamide was no greater than to 500 mgm. (After Moyer and Hughes (76), courtesy *J. Chronic Dis*)

occur, elimination of excessive extracellular fluid by increased sodium bicarbonate excretion is strictly limited, since bicarbonate and its associated cation represent only about 20 per cent of the extracellular electrolytes. The loss of excessive sodium bicarbonate and the resulting acidosis must be corrected by chloride loss before diuresis can be re-established. This may occur by excretion of chloride in association with ammonium ions during drug-free intervals. Apparently, this does not occur in serious cases of congestive failure and is the cause for failure of the drug to relieve the edema. Therefore, the agents are useful only for treating patients with mild congestive heart failure (89) or as maintenance therapy between parenteral mercurial injections for the treatment of severe congestive heart failure.

Other indications for these agents are pre-menstrual edema, and sodium and water retention during pregnancy when a low sodium intake is not sufficient to control this condition (25). The carbonic anhydrase inhibitors are not very satisfactory for the treatment of ascites due to cirrhosis and nephrosis. In the so-called "steroid edema," the use of carbonic anhydrase inhibitors is of very limited value because they produce a kaluresis, which may upset normal acid-base balance, since steroids also exert this same pharmacologic effect. In addition, for the treatment of this condition, it is necessary to use a diuretic which will produce a persistent diuresis for prolonged periods of time since the steroids are usually being administered continuously when this problem presents itself.

Acetazoleamide has been used with apparent success in the treatment of some types of epilepsy. When used for this purpose, the drug is administered at 8-hour in-

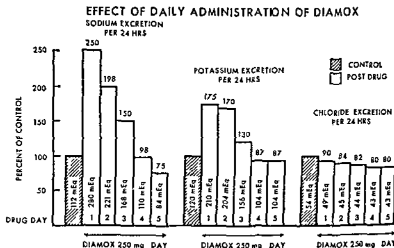


Figure 33 The maximum increase in sodium excretion occurs during the first day of acetazoleamide (Diamox) administration and declines continuously until the control rate of excretion is reached when administered daily (After Ford, Spurr and Moyer (34), courtesy *Circulation*)

Preparations and clinical use. Acetazoleamide, N.N.D., (Diamox) is available in 250 mgm tablets and ethoxzolamide (Cardrase) in 125 kg tablets. The minimal diuretic dose of each drug is approximately 40 mgm and almost the maximal diuretic action is attained with 125 mgm, so nothing is gained by using more than a 250 mgm dose.

The use of carbonic anhydrase inhibitors as oral diuretics has found clinical application in the treatment of mild edema due to numerous causes In patients with severe cardiac failure, acetazoleamide has almost uniformly failed to relieve the condition (82). In such patients, although the urine may become alkaline and potassium excretion increases, there is often little change in sodium excretion. Even when increased sodium excretion does

menstrual tension and edema, the drugs should be started with the onset of tension (usually 5 to 8 days before the onset of the menstrual period) in a dose of 125 to 250 mgm a day. It appears that these agents can be administered continuously until menses begins. In this instance, the results obtained by continuous daily administration for 5 to 8 days produces excellent therapeutic results.

Acidosis due to renal failure is a definite contraindication to the use of carbonic anhydrase inhibitors. These patients are not only unresponsive to the diuretic, but the effect on the carbonic anhydrase system throughout the body accentuates the acidosis and disastrous results may follow.

Side reactions. Side reactions to carbonic anhydrase inhibitors vary widely (Table XIII) and are dependent largely on the dose. Mild reactions are common. These consist of drowsiness and tingling and numbness of the face and extremities. *Lethargy, weakness, and leg pains are the* most common side effects. Since these reactions are not caused by sodium depletion, they must be a direct effect of the drug. Within equally effective therapeutic dose ranges the side effects to Cardrase, Diamox and Butamide are quite similar but the incidence of side reactions is much greater from Cardrase and Butamide than from Diamox. To avoid these reactions, the smallest dose of these compounds which will produce maximum diuresis should be used. The common side effects are presented in Table XIII.

tervals to maintain a mild state of metabolic acidosis. Whether the control of the condition is due to the acidosis or a direct central effect of the drug is not established.

From a practical point of view, the differences in therapeutic effectiveness between oral mercurials and carbonic anhydrase inhibitors is not so apparent when these agents are used in single doses. However, when continuous diuresis is mandatory, such as in patients with severe heart failure, mercurials become the agents of choice since these compounds continue to produce diuresis when administered daily. In contrast, the carbonic anhydrase inhibitors can be used only when an interrupted dosage schedule is feasible. One of the following dosage schedules for either ethoxzoleamide (Cardrase) or acetazoleamide (Diamox) should be employed, when these drugs are being used for the treatment of heart failure:

1) 250 mgm as a single dose daily for 2 or 3 successive days, allowing at least 2 days between courses of the drug. Single doses in excess of this amount should not be used. Larger doses produce no greater increase in sodium excretion but the excretion of potassium increases and this may result in potassium depletion.

2) 250 mgm as a single dose every other day. For maximal response, it is sometimes necessary to allow 2 days between drug administration. The correct dosage schedule can only be determined by trial and error on each individual patient. Mercurials should not be given concurrently, but may be given between courses of the carbonic anhydrase inhibitors.

When the carbonic anhydrase inhibitors are used for sodium and water retention associated with pregnancy, the drugs should be used in the same manner as for the treatment of heart failure. For the treatment of pre-

rate of chloride excretion (Figure 31). There is a moderate increase in the rate of potassium and bicarbonate excretion and little change in urinary pH (28, 32). The urinary electrolyte pattern is more characteristic of that seen during mercurial diuresis than that associated with carbonic anhydrase inhibition.

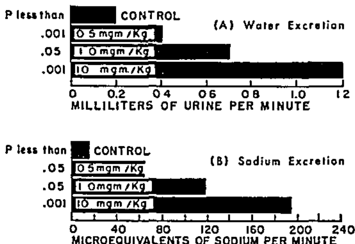


Figure 31A. Urine volume and sodium excretion after several different intravenous doses of chlorothiazide in dogs. (After Moyer, Ford and Spurr (71), courtesy *Proc Soc Exper. Biol & Med*)

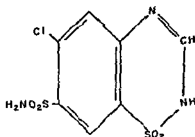
Following the administration of chlorothiazide, water excretion seems to be a secondary phenomena since not only the absolute excretion of sodium and chloride increase but the concentration of these electrolytes in the urine increases also. The greatest responses are seen during the second two-hour period following the oral ad-

Chapter 6

THE PHARMACOLOGY AND CLINICAL USE OF CHLOROTHIAZIDE

RECENTLY, a different type of carbonic anhydrase inhibitor has been introduced for use as a diuretic. Since it appears to have a different mechanism of action from the other agents of this class, it will be described separately.

Chemistry. Chlorothiazide (Diuril) is known chemically as 6-chloro-7-sulfamyl-1,2,4-benzothiodiazine-1,1-dioxide. It has the following structure:



Chlorothiazide is a colorless crystalline compound with a molecular weight of 295.7. It has a low solubility in water, but is readily soluble in dilute alkali.

Mechanism of action. Chlorothiazide is an effective inhibitor of carbonic anhydrase *in vitro*. This does not appear to be the primary mechanism for producing diuresis, however. With effective diuretic doses, the increased rate of sodium excretion is nearly balanced by an increased

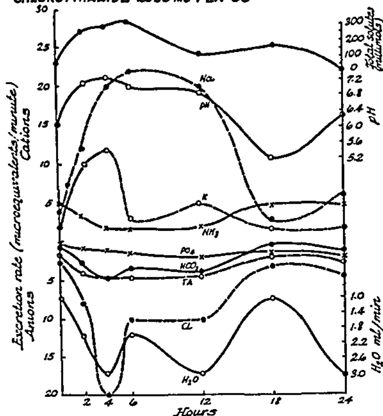


Figure 35. Electrolyte excretion pattern following the oral administration of a single 2000 mgm dose of chlorothiazide. (After Ford, Moyer and Spurr (29), courtesy *AMA Arch. Int Med*)

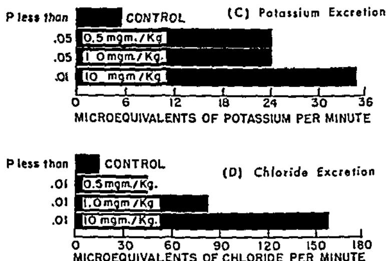


Figure 34B. Potassium and chloride excretion in the same dogs observed in Figure 34A. (After Moyer, Ford and Spurr (71), courtesy *Proc. Soc. Exper. Biol. & Med.)*

ministration of the drug (Figure 35) with persistence of the response at a lower level for 12 hours and return to control levels during the third 6-hour period (18 hours after the drug). As the dose of chlorothiazide is increased, the electrolyte excretion pattern becomes more characteristic of that observed with carbonic anhydrase inhibitors, i.e., there is an increasing rate of bicarbonate and potassium excretion.

Since therapeutic doses of chlorothiazide do not appreciably increase bicarbonate excretion, acidosis and resistance to the diuretic action do not develop on continued administration. In a patient who received 2 grams of

chlorothiazide orally at 6 a. m. daily the maximal increase in the rate of sodium excretion occurred on the second day (Figure 37A, B). However, there was a declining excretion of sodium on the fourth and fifth days as the body stores of this electrolyte were depleted. The excretion rate of sodium gradually declined until it approximat-

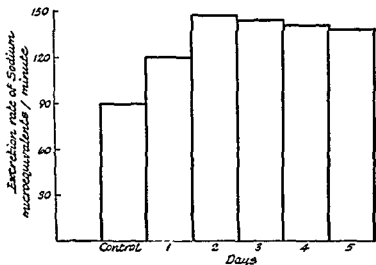


Figure 37A. When chlorothiazide is administered daily in a single 2000 mgm oral dose, the maximum rate of sodium excretion occurs on the second day and this high rate is maintained until body stores of sodium become depleted. Observations made on a non-cardiac patient maintained on a diet containing 150 mEq of sodium. (After Ford, Moyer and Spurr (29), courtesy *AMA Arch. Int. Med*)

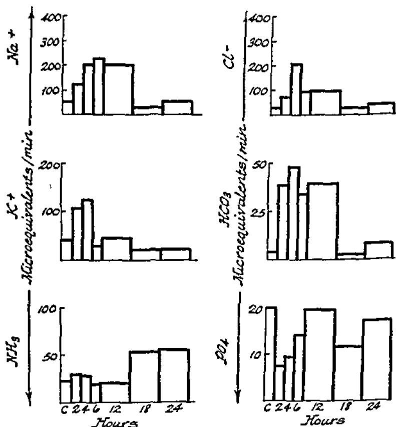


Figure 36. Typical electrolyte excretion patterns after oral administration of 2000 mgm of chlorothiazide (After Moyer, Ford and Spurr (70), courtesy *AMA Arch. Int. Med.*)

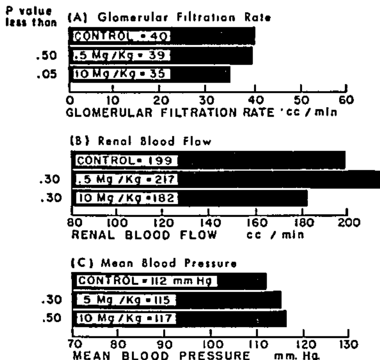


Figure 38. Renal hemodynamic response to intravenous chlorothiazide (Diuril) in the dog. (After Moyer, Ford and Spurr (71), courtesy *Proc Soc Exper. Biol & Med*)

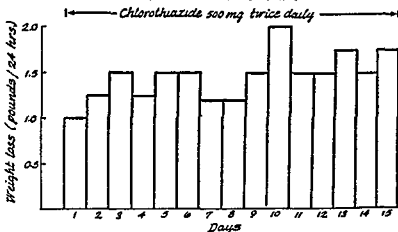


Figure 37B. Weight loss in edematous patients parallels the increase in sodium excretion following the administration of chlorothiazide. The diuretic response is maintained as long as the drug is given. (After Ford, Moyer and Spurr (29), courtesy *AMA Arch. Int. Med.*)

ed the sodium intake and remained there as the patient approached dry weight.

During the onset of diuresis from chlorothiazide, there is no significant change in glomerular filtration rate or renal plasma flow (Figure 38). Diuresis must be, therefore, attributed to an inhibitory effect on the mechanisms for reabsorption of water and electrolytes. With large doses, carbonic anhydrase inhibition undoubtedly is partly responsible for diuresis. This mechanism probably has a minimal effect at the lower effective dosage levels.

Chlorothiazide has been reported to enhance the hypotensive effect of various agents used in the treatment

The action persists for about 12 hours after oral administration.

In a patient who received the drug at a dose of 1000 mgm twice within a 24-hour period the increase in the excretion rate of sodium was repeated after the second dose in a fashion similar to that following the first dose but at a higher level (Figure 41) and the total increase in sodium excretion per 24 hours after receiving 1000 mgm every 12 hours was greater than after a single dose of 2000 mgm. It appears that when given every 12 hours, the first 2 or 3 doses are cumulative but that on continued administration of the drug each subsequent dose does not produce a greater diuresis.

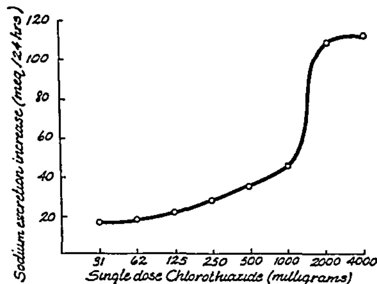


Figure 40 Dose-response curve from orally administered chlorothiazide in a patient with congestive heart failure. (After Moyer, Ford and Spurr (70), courtesy *AMA Arch. Int. Med.*)

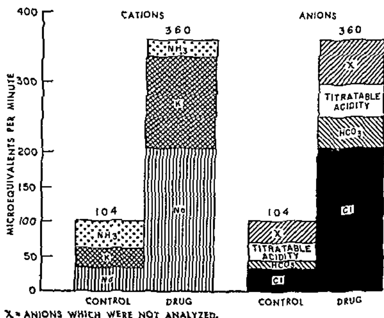


Figure 39. Average rate of excretion of various ions per minute after 2000 mgm of chlorothiazide in a cardiac patient (based on a 24-hour urine collection). (After Moyer, Ford and Spurr (71), courtesy *Proc Soc Exper. Biol & Med.*)

of hypertension and even to have a hypotensive effect when used alone (50). This latter effect is controversial.

Absorption. The onset of action from chlorothiazide is prompt, indicating rapid absorption from the gastrointestinal tract. There is an increased diuretic and natriuretic response from this agent in patients as the oral dose is raised to approximately 4000 mgm (Figure 40). Increasing the dose above this amount produces little additional effect.

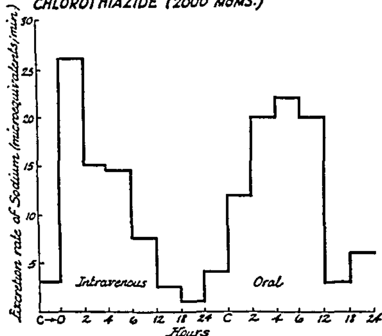


Figure 42. The onset of action is slower but more prolonged following the oral administration of chlorothiazide in comparison with an intravenous dose. (After Ford, Moyer and Spurr (29), courtesy *AMA Arch Int. Med*)

In patients who have received 2000 mgm intravenously over a 60-minute period, the pattern of sodium excretion was similar to that following the oral dose but was earlier in onset, shorter in duration, and hence less effective (Figure 42). In the absence of gastrointestinal disease the oral route of administration is to be preferred, an attribute of note with any therapy requiring continuous drug administration.

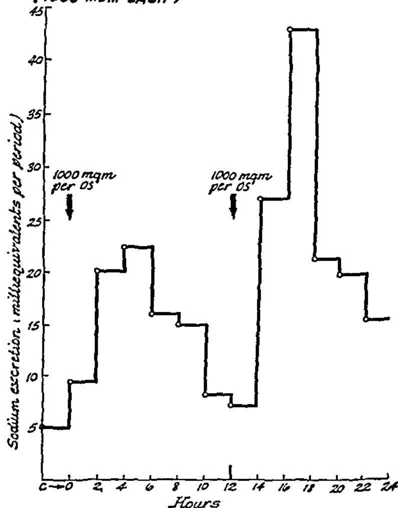


Figure 41. When chlorothiazide is given at 12-hour intervals the second dose produces a greater increase in sodium excretion. This additive effect reaches a maximum on the second day. (After Ford, Moyer and Spurr (29), courtesy *AMA Arch. Int. Med.*)

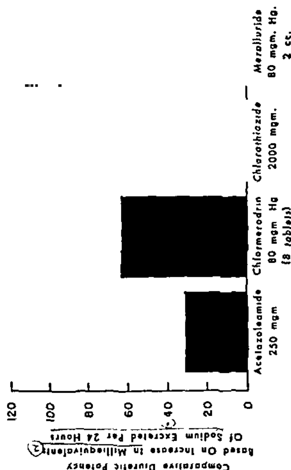


Figure 44. Comparative potency of different diuretics

tinued treatment. Uncommon side reactions include muscle cramps, giddiness, paresthesias, and dermatitis.

Comparative Potency. When potency of chlorothiazide is compared with other diuretics (Figure 44 and Table

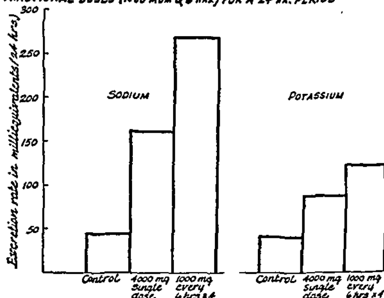


Figure 43. The effect of a single oral dose of chlorothiazide and an equivalent amount given in divided doses over a 24-hour period. (After Moyer, Ford and Spurr (70), courtesy *AMA Arch. Int. Med.*)

Fate and excretion. Chlorothiazide disappears slowly from the plasma in nephrectomized dogs which indicates that the compound may be partially transformed metabolically. It has been isolated from the urine and feces so that degradation is not complete. The rate of clearance by the kidney is greater than the glomerular filtration rate which indicates tubular secretion of the compound.

Toxic reactions. Chlorothiazide is usually well tolerated. Moderate muscular weakness and fatigue may appear initially but these symptoms usually disappear with con-

clinical conditions are congestive heart failure, premenstrual edema, edema of pregnancy, hepatic disease, and the iatrogenic edema associated with the therapeutic administration of steroids. In addition, it may prove to be the most effective agent for the treatment of edema associated with renal disease, although this has not been well substantiated as yet.

Congestive Heart Failure. Chlorothiazide has been administered to approximately 200 patients in our clinic for a period of one year. It has proven to be an effective therapeutic agent devoid of serious untoward reactions when used in doses of 250 to 4000 mgm daily. Several patients complained of lethargy and weakness during the period of maximum diuresis. It appears to be useful for both initial and maintenance therapy in congestive heart failure.

For patients who have significant sodium and water retention and in whom immediate diuresis is indicated, a dose of 1000 mgm should be given every 8 hours. If the degree of diuresis is excessive, the dose can gradually be reduced to as little as 500 mgm per day. Doses less than 250 mg produce no diuretic response and patients receiving less than this amount would do equally well by receiving a placebo.

As the patient approaches "dry weight," the dose of the drug should be reduced gradually until the minimal effective dose has been ascertained. When the dose requirement is less than 500 mgm every other day, such a patient could probably do equally well on a low sodium diet alone. With the use of chlorothiazide in patients who are not in intractable or terminal heart failure, the dietary intake of sodium can be liberalized. It is not necessary to discontinue the drug intermittently for con-

14), it appears that a dose of 40 mgm of mercury equivalent of meralluride (1 cc) administered parenterally produces an increase in sodium excretion that is equivalent to 1138 mgm of chlorothiazide administered orally, and 683 mgm of chlorothiazide is equal to 4 tablets, or 40 mgm of chlormerodrin Hg (Neohydrin). This dose is approximately twice as effective as acetazoleamide (Diamox) at its maximally effective dose.

TABLE XIV

COMPARATIVE POTENCY OF CHLOROTHIAZIDE AND VARIOUS MERCURIAL DIURETIC AGENTS. (After Ford, Moyer, and Spurr (29), courtesy *Arch Int Med.*)

Drug	*Route of Administration*	*Potency Estimation**	*Dose (mgm) Oral Chlorothiazide Equivalent to 40 mgm (Hg) of the Mercurial Agent (1 cc. of Parenteral Drugs and 4 Tablets of Oral)*
Diglucomethoxane (Mersoben)	I.M	1 3	1480
Meralluride (Mercuhydrin)	I.M	1 0	1138
Mercaptomerin (Thiomerin)	I M	0 6	683
Chlormerodrin (Neohydrin)	Oral	0 5	569
Chlorothiazide (Diuril)	Oral	0 8	—

* Determined from previous analysis of variance of these drugs (Ford, *et al*, The Problem of Bioassay and Comparative Potency of Diuretics. I. Parenteral and Oral Mercurial Diuretics. *Circulation*, submitted for publication).

Clinical use of Chlorothiazide. Clinical experience indicates that the drug can effectively replace currently available orally and parenterally administered diuretic agents in the management of various disease entities associated with sodium and water retention. The most important of these

Renal disease. Chlorothiazide has been administered to patients with the nephrotic syndrome of all grades of severity. It is of limited value when used for this purpose, as are all diuretics. It is no more effective than intramuscular meralluride (Mercuhydrin) given in doses of 1 cc every 12 hours. An occasional patient with this disease reacts dramatically to chlorothiazide, whereas in others it is completely ineffective. It is not possible to predict which patients will respond. When chlorothiazide is used for promoting diuresis in patients with nephrosis, it is mandatory that the drug be given no less frequently than every 12 hours and a 6 to 8 hour interval is preferable. Five hundred mgm should be given at each dose initially and depending on the response, the dose may be increased to a maximum of 2000 mgm.

Iatrogenic Steroid Edema. In our experience, chlorothiazide is one of the most effective agents for preventing sodium and water retention associated with the administration of adrenal cortical steroids It does not prevent the development of "moon face" and care must be taken that hypokalemia does not occur, since the adrenal steroids themselves tend to promote increased potassium excretion The concurrent administration of chlorothiazide enhances this response. Potassium should be administered, along with the diuretic (3 to 5 grams of KCl daily) in order to prevent the occurrence of this complication.

When administered for preventing steroid edema, 500 to 1000 mgm should be given orally every 8 to 12 hours. The minimally effective dose should be used. This is particularly important in this instance since the larger the dose the greater the kaluretic effect and the greater the possibility that hypokalemia will occur.

tinued therapeutic effectiveness since tolerance to the drug does not occur.

Chlorothiazide may be administered intravenously in doses of 1000 mgm over a 5-minute period without untoward effects. However, the dose requirements by this route are as large as by the oral route. The drug should be given intravenously only when drug administration by the oral route is contraindicated.

Edema associated with hepatic disease. Chlorothiazide is effective in promoting sodium and water excretion in patients with cirrhosis. It is somewhat more effective than daily administration of mercurial diuretics by the parenteral route.

Usually diuresis occurs during the first 8 to 10 days of continuous administration of chlorothiazide. The weight then frequently levels off despite the presence of residual edema or ascites and further sodium and water depletion does not occur. A patient will usually remain at this weight level with continued drug administration but when therapy is stopped, additional sodium and water retention follows within several days.

For sodium and water retention associated with cirrhosis, chlorothiazide should be given in doses of 1000 mgm every 8 to 12 hours. When given less frequently, the drug is less effective. Although a diuretic response is observed after each dose when given at widely spaced intervals, sodium and water retention occur between doses and the net loss of water and sodium is less significant.

Chlorothiazide has not been observed to produce untoward effects when administered to patients with cirrhosis. Apparently, the drug has no adverse effect on hepatic function, even in the presence of liver disease.

tered concurrently with ganglionic blocking agents the orthostatic blood pressure effect continues.

2) If the blood pressure is to be well regulated, the dose of the ganglionic blocking agent must be reduced but these agents must usually be continued in those patients in whom there was a real indication for the blocking agent in the first place.

3) The blood pressure response to the combination of chlorothiazide and ganglionic blockade is just as variable as it is when the blocking agent is administered alone.

4) The side effects from the combination of ganglionic blockade and chlorothiazide are the side effects that are observed with the use of ganglionic blocking agents, i.e., orthostatic blood pressure reduction and parasympathetic blockade.

5) When the dose of chlorothiazide is reduced below 250 mgm the effect of enhancing the hypotensive response to antihypertensive agents is usually lost. This dose of chlorothiazide is also the threshold dose for a natriuretic and diuretic response.

Therapeutic Use in Hypertension. When initiating therapy for hypertension, it now seems justifiable to routinely use a combination of a natriuretic agent along with drugs which depress the sympathetic nervous system in those patients in whom drug therapy is indicated. A recommended therapeutic schedule is to start the patient on 250 mgm of chlorothiazide every 12 hours and continue this dose for three days. In the absence of serious untoward reactions, the dose should then be increased to 500 mgm twice a day. This dose of chlorothiazide should be continued indefinitely in combination with specific antihypertensive agents. After one week, some form of Rauwolfia

Chlorothiazide in Hypertension. Recently, it has been observed that chlorothiazide will enhance the response to antihypertensive agents. For example, when chlorothiazide is given in conjunction with any of the ganglionic blocking agents, the dose requirement of the blocking agent is reduced approximately 50 per cent or more in about three-fourths of the patients. In the remaining one-fourth, no effect on blood pressure or dose requirement of the blocking agents is observed. The mechanism whereby this is accomplished is not completely understood. However, similar effects, although not as pronounced, are also observed with other diuretic and natriuretic agents, such as chlormerodrin (Neohydrin), when given in adequate doses continuously. The side effects with chlorothiazide are less marked than with the oral mercurial diuretics. This makes it more feasible to use this agent on a long-term basis in conjunction with antihypertensive agents.

Whatever the mechanism of its action, it appears that chlorothiazide may prove to be an important adjunct in the treatment of hypertension. It is too early to evaluate the long-term effect of this form of therapy for hypertension. Whether the potentiation of ganglionic blockade produced by chlorothiazide is shared equally by other effective diuretics is at present not known. It is our feeling, however, that the action is not specific and depends on natriuresis. With the introduction of new effective relatively nontoxic diuretics this problem demands further investigation.

It may be concluded that:

1) Chlorothiazide potentiates the action of Rauwolfia compounds and ganglionic blocking agents and will probably prove to be a valuable adjunct in the management of hypertensive diseases. When it is adminis-

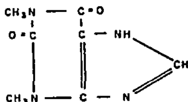
above. The dose of the ganglionic blocking agent must be readjusted according to the desired blood pressure level.

should be started, such as 1 mgm of reserpine, 8 mgm of alseroxylon or 300 mgm of the whole root. This dose should be continued for one week and then reduced by one-half. When the response to chlorothiazide and Rauwolfia is inadequate and the use of more potent agents seems to be justified, a ganglionic blocking agent should be started according to the usual dose titration procedure for the drug being employed.

When the hypotensive response is inadequate from Rauwolfia alone or used in combination with a ganglionic blocking agent in patients who have already been taking these drugs, chlorothiazide can be added to the regimen to increase the antihypertensive effect. When the hypotensive response to Rauwolfia alone is inadequate, chlorothiazide should be added in a dose of 250 mgm twice a day for three days. If the response continues to be inadequate, the dose of chlorothiazide should be increased to 500 mgm twice a day and continued indefinitely. The patient should be receiving one of the Rauwolfia alkaloids in a dose amounting to at least 0.5 mgm of reserpine, 4 mgm of alseroxylon or 150 mgm of the whole root. When the response is inadequate after two weeks, then a ganglionic blocking agent can be added when indicated.

A patient already receiving a ganglionic blocking agent should be given chlorothiazide with care. The initial dose of chlorothiazide is 250 mgm given twice a day. In those patients who were partially responsive to the ganglionic blocking agent, it frequently becomes necessary *to reduce the dose of the blocking agent on the average of 50 per cent. The chlorothiazide should* be increased to 500 mgm after one week and continued at this dose level indefinitely. When Rauwolfia is part of the program it should be continued at the dose indicated

forms are generally employed therapeutically. The chemical structure of theophylline is given below.



Mechanism of action of xanthines. A vast amount of controversial literature has accumulated concerning the mechanism of diuresis from the xanthines (86). Undoubtedly, much of the confusion has resulted from faulty techniques.

The xanthines are known to have a stimulant action on the myocardium and increase the cardiac output, stroke volume, and heart rate (100). Diuresis from these compounds has been ascribed to improvement in renal blood flow and glomerular filtration secondary to the cardiac effects. These agents do frequently increase renal blood flow in both animals and human subjects, as has been demonstrated by renal clearance techniques. Nevertheless, diuresis can frequently be demonstrated with little or no detectable change in the renal circulation (Table XV). Furthermore, when an increase in renal blood flow does occur, diuresis often outlasts the circulatory effect. Similarly, changes in glomerular filtration rate do not parallel the degree of diuresis induced.

Probably, a direct renal tubular effect is the most important factor responsible for xanthine diuresis. Conclusive evidence for a direct renal effect was first presented by unilateral renal artery injection of a theophylline preparation in the dog (3,14). In these investigations, the injection of a small amount of a theophylline

Chapter 7

THE PHARMACOLOGY AND CLINICAL USE OF XANTHINE AND ISOCYTOSINE DIURETICS

XANTHINE derivatives, such as aminophylline and various salts of theobromine, have long been familiar adjuncts in cardiac failure therapy. Despite much lower diuretic potency than other agents, the xanthines are still used extensively in edematous states. This is probably a reflection of the absence of serious untoward reactions from these compounds and the unavailability of effective oral diuretics until comparatively recently.

Theophylline solubilized by reacting it with ethylenediamine (aminophylline) is the xanthine most commonly used as a diuretic. It has a more prompt but less sustained action than theobromine.

Aminometradine (Mictine) and aminoisometradine (Rolicton) are two isocytosine compounds recently introduced for use as oral diuretics. These xanthine related compounds are derivatives of the pyrimidine base cytosine which occurs in nucleic acid.

Chemistry. The xanthines are derivatives of purine which is found in nucleic acid. The free bases are sparingly soluble in water. They may be readily made soluble by combination or admixture with other substances. Soluble

salt produced diuresis in the injected kidney, but not in the uninjected one. A large amount of evidence has now accumulated to indicate that the only consistent renal effect from aminophylline is a depression of water, sodi-

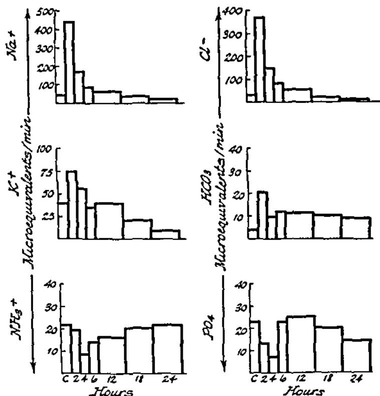
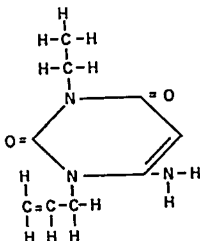


Figure 45 Electrolyte excretion in a cardiac patient following the intravenous administration of 500 mgm of aminophylline (After Ford, Moyer, Handley, Spurr and Rochelle, (28), courtesy *Am. J. Med. Sci.*)

TABLE XV

THE EFFECT OF AMINOPHYLLINE ON RENAL FUNCTIONS. Female subject, 70.5 kgm. (After Moyer (64), courtesy *Pharmacology in Medicine* V A Drill, Ed, Blakistan Div, McGraw-Hill Book Company).

Time Min	*Urine Volume cc. Per Min*	*Glomerular Filtration Rate, cc Per Min*	*Renal Plasma Flow, cc. Per Min.*	*Sodium Excretion, mEq. Per Min.*
		CONTROL		
0-10	3 5	102	630	0.238
10-20	3.7	99	635	0.229
20 38				
		Aminophylline, 500 mgm I.V.		
38-48	15 9	99	604	0.823
48 58	13 1	100	591	0 618
58 68	11 9	98	597	0 563



These compounds are white, crystalline, water soluble substances.

Mechanism of action of isocytosines. Aminophylline and the aminometradines have a similar effect on renal transport mechanisms for various electrolytes. All three cause increased rate of excretion of sodium and chloride, slight inhibition of ammonia and phosphate excretion (Figure 45 and 46) without consistent changes in potassium and bicarbonate excretion. The per cent increase in the rate of sodium excretion is usually somewhat greater than that for water (29).

The exact mechanism of action of these compounds on the renal transport mechanisms is unknown. Diuresis is probably caused by a partial inhibition of the sodium and chloride reabsorbing mechanisms in the cells of the renal tubule. The increase in volume of water excreted during diuresis may tentatively be assumed to be secondary to the increased concentration of sodium and chloride ions in the tubular fluid.

um and chloride reabsorption. This would appear to indicate that the xanthines partially inhibit the mechanisms in the cells of the renal tubules that are responsible for reabsorbing these constituents from the glomerular filtrate. It cannot be denied that renal hemodynamic changes can occur from these agents and may contribute to their diuretic action. These changes do not, however, appear to be essential for diuresis.

Absorption, fate and excretion of xanthines. The xanthines are rapidly absorbed from the gastrointestinal tract and after intramuscular administration of soluble salts. They undergo demethylation in the body and the degradation products are excreted in the urine.

Development of tolerance is a characteristic feature of the xanthines on continued administration. After the development of tolerance to one member of the group there is cross-tolerance to the other members.

Toxicity of xanthines. The xanthines are relatively nontoxic compounds Nausea and vomiting due to gastric irritation is a common side effect. Intravenous administration of aminophylline has been known to produce ventricular fibrillation.

Chemistry of isocytosines. The chemical name of aminometradine is 1-Allyl-3-ethyl-6-aminotetrahydropyrimidinedione. Aminoisometradine is 1-methallyl-3-methyl-6-aminotetrahydropyrimidinedione. The chemical structure of aminometradine is as follows:

(administered orally) can be demonstrated to have a mild diuretic and natriuretic but the incidence of side reactions is excessively high at effective doses, i.e., 1200 mgm per day or more. In a study completed by the authors and their associates, at this 1200 mgm dose, the increase in sodium

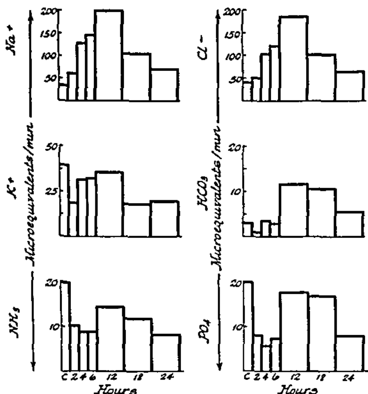


Figure 46 Electrolyte excretion in a cardiac patient following the oral administration of 1600 mgm of aminoisometradine (Rolicton) (After Ford, Moyer, Handley, Spurr and Rochelle (28), courtesy *Am. J. Med Sci*)

Glomerular filtration rates are not altered when either aminometradine or aminoisometradine are given intravenously to dogs. Occasionally, a moderate increase in renal plasma flow is observed (28).

Onset and duration of action of isocytosines. When given intravenously to dogs in doses of 25 mgm per kgm, *diuresis begins within 30 minutes, reaches a maximum in* about one and one half hours and begins to subside in about 3 hours. Administered orally in the same dosage, diuresis begins within one hour, reaches a maximum in approximately 4 hours and persists for 7 or 8 hours. In humans, orally administered doses of these compounds produce maximal diuresis in 6 to 12 hours. The average increase in the rate of sodium excretion in ten patients was 62 mEq per 24 hours with aminoisometradine and 89 mEq per 24 hours with aminometradine.

Tolerance to the isocytosines does not develop as readily on continuous administration as it does with the xanthines.

Absorption, fate and excretion of the isocytosines. Absorption appears to be adequate from the gastrointestinal tract. No studies have been reported on metabolic changes that these compounds may undergo in the body or channels of excretion

Toxicity of isocytosines. The most common side effects from these agents are nausea, vomiting and diarrhea. Less commonly, dizziness and various types of cutaneous rashes may occur. Leucopenia has been reported following the administration of aminoisometradine.

Clinical use of xanthines and isocytosines. Compared to currently available drugs for oral use, aminophylline

(administered orally) can be demonstrated to have a mild diuretic and natriuretic but the incidence of side reactions is excessively high at effective doses, i.e., 1200 mgm per day or more. In a study completed by the authors and their associates, at this 1200 mgm dose, the increase in sodium

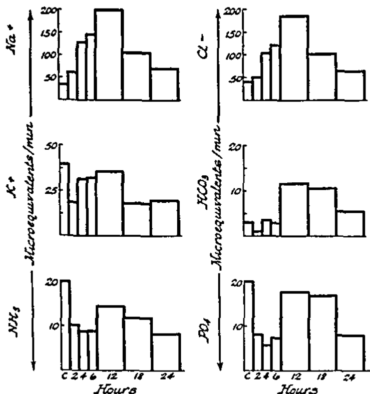


Figure 46 Electrolyte excretion in a cardiac patient following the oral administration of 1600 mgm of aminoisometradine (Rolicton) (After Ford, Moyer, Handley, Spurr and Rochelle (28), courtesy *Am J Med Sci*)

excretion was only 41 mEq per 24 hours with patients on a 50 mEq sodium diet, yet toxicity occurred in more than 25 per cent of the patients receiving the drug (24). Consequently, this compound is of little value for use as an orally administered diuretic agent. However, when given intravenously the drug is more effective and may (Figure 45) be useful in acute states of cardiac decompensation, although the response is lost within four hours. The drug may also be useful for temporarily increasing glomerular filtration rate (10) and thus increasing the effectiveness of parenterally administered organomercurial diuretics. For this purpose, aminophylline sholuld be given one hour after the mercurial was given by the intramuscular or intravenous route. Potency estimation studies indicate that intravenously (or orally) administered aminophylline is less than 0.5 as potent as meralluride given intramuscularly. Aminometradine and aminoisometradine given orally are 0.7 and 0.5 as potent respectively as meralluride given intramuscularly Comparatively speaking, one cc of meralluride is equivalent to approximately 1600 mgm of aminoisometradine and approximately 850 mgm of aminometradine in the production of an increased natriuresis.

Aminometradine and aminoisometradine are both useful oral diuretics, since both are effective natriuretic agents when adequate doses are employed. The maximum effective single dose which will not produce excessive side reactions (i.e., side reactions occur when given as a single dose in less than 25 per cent of patients treated), is 1600 mgm for aminoisometradine and 1200 mgm for aminometradine. The comparative effect from these doses is shown in Table XVI which summarizes the observations on 10 patients studied under controlled metabolic conditions (28). Using these same conditions, the

TABLE XVI

EFFECTS OF AMINOISOMETRADINE AND AMINOMETRADINE ON SODIUM EXCRETION. (After Ford, Moyer, Handley, Spurr and Rochelle (28), courtesy *Am. J. Med. Sci.*)

			Aminoisometradine			
800 mgm				*1600 mgm*		
C	*D*	*I*		*C*	*D*	*I*
50	55	5		45	103	58
45	53	8		50	120	70
50	70	20		45	105	60
48	64	16		50	98	48
43	50	7		45	104	59
50	64	14		49	108	59
44	57	13		50	115	65
50	56	6		45	106	61
50	58	8		42	112	70
45	68	23		48	115	67
48	60	12	*Average*	47	109	62
			Aminometradine			
600 mgm				*1200 mgm*		
C	*D*	*I*		*C*	*D*	*I*
44	90	46		46	161	115
48	102	54		49	181	132
44	90	46		43	146	103
46	66	20		45	120	75
43	69	26		47	130	83
47	86	39		46	166	120
45	83	38		42	86	44
42	67	25		44	110	66
49	105	56		46	160	114
40	66	26		40	77	37
45	83	38	*Average*	45	134	89

C — Control—mEq sodium excretion/24 hours
D — Drug—mEq sodium excretion/24 hours
I — Increase—mEq sodium excretion/24 hours

threshold dose (minimally effective dose) of aminoisometradine was 800 mgm and the threshold dose of aminometradine was 400 to 600 mgm (Table XVI).

Because of the limited potency of aminometradine and aminoisometradine, these compounds are relegated to

use in the treatment of patients with only mild heart failure or in other conditions which yield to therapy with the less potent diuretic agents. They may also be used for prolonging the period between injections of the more potent parenterally administered organomercurials in patients with moderately severe to severe heart failure. They are useful in such varied conditions as portal cirrhosis, premenstrual edema, edema of pregnancy, occasionally in kidney disease, venous stasis, etc.

When these compounds are used on a divided dosage schedule, 400 mgm of aminometradine four times daily and 600 mgm of aminoisometradine four times daily usually do not produce prohibitive side effects. When nausea becomes a serious problem, decreasing the dose or using an interrupted schedule will effectively relieve this side effect in most instances. For an interrupted schedule, the drugs may be given for 2 to 3 days followed by withdrawal for a similar period of time. The drugs should be given with meals or immediately following in order to minimize gastrointestinal side effects.

TABLE XVII

SIDE EFFECTS OF AMINOMETRADINE AND AMINOISOMETRADINE IN 122 PATIENTS WITH HEART FAILURE

	Aminometradine (1200 mg/day)	*Aminoisometradine (1600 mg/day)*
Nausea	16	12
Vomiting	8	6
Anorexia	12	10
Diarrhea	4	2
Abdominal cramps	8	4
Flatulence	3	2
Skin rash	2	2
Dizziness	2	3
Headache	15	11

Although the incidence of side effects is less with aminoisometradine than from the same dose of aminometradine (Table XVII), the former drug is less potent (Figure 47). Consequently, when doses of each drug are given which produce an equivalent diuretic and natriuretic response, the incidence and severity of side reactions are almost identical, according to our observations.

The dosage schedule should be regulated by the diuretic response observed. The usual starting dose of ami-

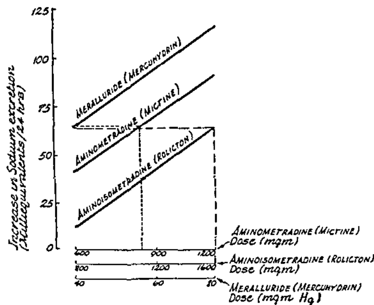


Figure 47. Dose response curves of aminometradine aminoisometradine compared with meralluride. (After Ford, Moyer, Handley, Spurr and Rochelle (28), courtesy *Am J Med Sci*)

noisometradine is one tablet (200 mgm) with each meal. This dose is increased if the diuretic response is inadequate. As much as 3 to 4 tablets (600 to 800 mgm) may be given with each meal. Doses in excess of this amount are frequently associated with excessive side reactions.

Although it has been reported that tolerance to these compounds does not develop, this assertion is not consistent with our experience. We have observed that the drug is considerably less effective on the fourth to fifth day of drug administration than on the first and second. Consequently, it is best to use an interrupted dosage schedule. When such a schedule is not adequate it is best to use a supplementary dose of another diuretic such as chlorothiazide or one of the organomercurial diuretics.

There is no evidence to indicate that renal or hepatic disease presents a contraindication to the use of the isocytosines.

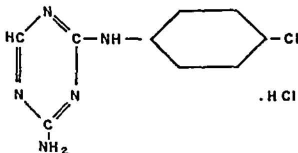
Chapter 8

THE PHARMACOLOGY AND CLINICAL USE OF TRIAZINES

A NUMBER of triazine derivatives have been studied for their possible effectiveness as oral diuretics. Attention was first directed at the diuretic activity of this group of compounds a number of years ago (57). Formoguanamine, the most potent compound of the series found in these early studies, proved to be impractical for therapeutic use because of its tendency to produce renal damage.

Recently, exploration of new triazine derivatives has uncovered two with diuretic activity and comparatively low toxicity (112, 68). One has been given the generic name of chlorazanil and the other is designated as UX-6.

Chemistry. Chlorazanil (Daquin) is n-p-chlorophenyl-2,4-diamino-s-triazine and has the following structural formula:



It is a white, crystalline, and tasteless compound and is a weak base. The free base is sparingly soluble in water but forms soluble salts with mineral acids. For diuretic activity, the chlorine atom must be in the para position.

UX-6 is 2-amino-4-isoamylamino-s-triazine hydrochloride. It is a white crystalline compound and is freely soluble in water.

Mechanism of action. The mechanism by which the triazines produce diuresis has not been clarified. In both animals and man, these agents produce a consistent and rather prolonged increase in the rate of sodium excretion. Chlorazanil is more potent in this respect Although the rate of chloride excretion is also increased, the effect on this ion is not as great as on sodium The excretion of bicarbonate is also enhanced but the order of magnitude is roughly one-tenth to one-fourth that of chloride and this effect is not consistently observed. Urinary pH is slightly increased while titratable acidity, phosphate and ammonia excretion may be slightly depressed during the maximal drug effect. The excretion of potassium is increased slightly for a short period of time as diuresis develops. The percentage increase in water and sodium excretion is approximately the same after these triazines, whereas with other diuretics, the effect on sodium excretion is greater. Plasma concentrations of sodium, potassium, chloride and bicarbonate and blood pH are not altered after daily administration of the compounds for several days (32, 68).

From the changes in electrolyte excretion during chlorazanil diuresis, it may tentatively be assumed that several mechanisms are involved. The increased excretion of bicarbonate suggests that the compounds may produce some degree of carbonic anhydrase inhibition. This effect must be weak, if it occurs, because urinary pH and

the excretion of titratable acids and ammonia are not greatly altered as they are with the sulfonamide derivatives. Also, acidosis does not develop on continued administration. Furthermore, ammonium chloride produces an additive effect when given with chlorazanil while it inhibits the diuresis from carbonic anhydrase inhibitors. Glomerular filtration rate and renal blood flow (Figure 48) are not altered by the triazines so that changes in renal hemodynamics are not involved in the diuretic effect.

Onset and duration of action. When chlorazanil is given intravenously to dogs, diuresis begins within twenty minutes and persists for more than five hours. With oral administration, the diuretic effect is not as dramatic but the duration is much longer The onset of diuresis occurs

THE EFFECT OF CHLORAZINIL ON RENAL HEMODYNAMICS
AVERAGE VALUES FOR 8 DOGS (8 mgm / kgm IV.

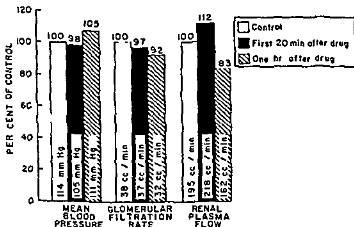


Figure 48. Renal hemodynamic response to chlorazanil Average values for 8 dogs (8 mgm/kgm, I V). (After Ford, Rochelle, Spurr, Handley and Moyer (32).)

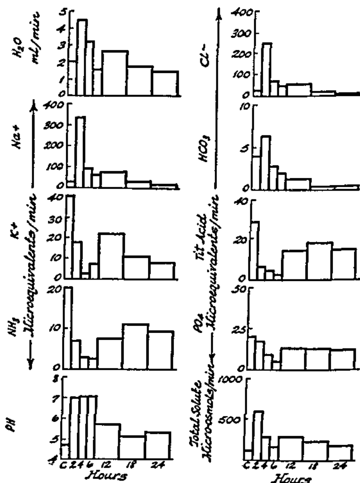


Figure 49. Excretion patterns following the oral administration of 600 mgm of chlorazanil to a cardiac patient. (After Ford, Rochelle, Spurr, Handley and Moyer (32).)

approximately two hours after oral administration to cardiac patients (Figure 49) and persists for 12 to 18 hours. Chlorazanil continues to be effective with daily administration in both animals and cardiac patients until the sodium load has been depleted.

A comparison with other orally active non-mercurial diuretics indicates that chlorazanil is more potent than acetazoleamide (Diamox) but less potent than chlorothiazide (Diuril).

Absorption, fate and excretion. Little information is available concerning the rate of absorption, fate and rate of excretion of chlorazanil. The observation that diuresis begins within two hours after oral administration indicates that it must be rapidly absorbed from the intestinal tract. In rats, 75 per cent of the administered dose can be recovered from the urine in 24 hours.

Toxicity. The LD_{50} in rats is less than 20 mgm per kgm when administered daily for a period of two weeks by the intraperitoneal route. Rats seem to be particularly sensitive to the drug since daily oral administration of up to 50 mgm per kgm in dogs produced no signs of toxicity No gross or microscopic changes were observed in these animals on autopsy.

Clinical use of triazines. Although UX-6 showed definite diuretic effect when administered to patients in heart failure who were being studied under controlled metabolic conditions (68), this response was not adequate to control ambulatory patients who were in heart failure

two-thirds as effective as acetazoleamide (Diamox). Per-

haps the inability to effectively control these patients was due to the poor natriuretic effect of the drug. Eight hundred mgm per day of the drug was no more effective than 400 mgm and only slightly more effective than 200 mgm (68).

When out-clinic patients, who received this drug for one month or more, were given 2 cc of meralluride, nearly all of them lost weight, indicating sodium and water retention during UX-6 therapy. Side effects primari-

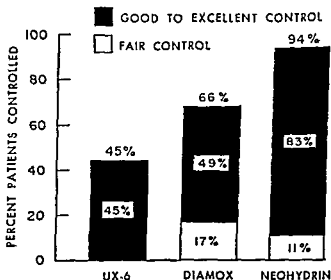


Figure 50A. A comparison of results of UX-6 therapy with Diamox and Neohydrin in similar patients with congestive heart failure. (After Moyer, Ford and Handley (68), courtesy *AM & CT*.)

DURATION OF CONTROL OF CONGESTIVE FAILURE IN 11 PATIENTS TREATED WITH UX-6 DIURETIC ALONE

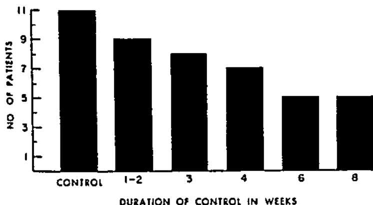


Figure 50B Duration of control of congestive heart failure in 11 patients treated with UX-6 alone (After Moyer, Ford and Handley (68), courtesy *AM & CT*)

ly consisted of sedation, anorexia, nausea, fatigue and weakness.

Chlorazanil has proven to be a more effective diuretic than UX-6. The natriuretic effect, although less marked than the diuretic effect, was significant Following the administration of 300 mgm as a single dose to 10 patients, sodium excretion increased an average of 11 mEq per 24 hours, but after a dose of 600 mgm, the increase was 60 mEq per 24 hours (Figure 51).

Chlorazanil continued to be effective with daily administration (Figure 52) of 300 mgm as determined by sodium and water excretion

Comparing the potency of chlorazanil and meralluride revealed that chlorazanil is about 50 per cent as

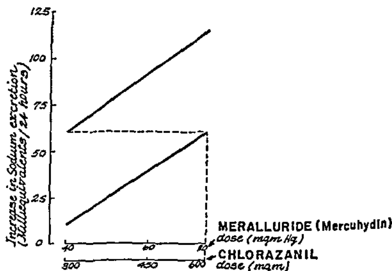


Figure 51 Dose-response curves showing potency of chlorazanil in comparison with meralluride (After Ford, Rochelle, Spurr, Handley and Moyer (32), courtesy *J Clin. Invest.*)

potent as meralluride as a natriuretic agent but two times as potent as a diuretic agent, indicating a greater effect on water excretion (Figure 52). The drug is more potent than acetazoleamide but not as potent as chlorothiazide.

Side reactions consist primarily of nausea and vomiting. These are of little consequence when the dose is not more than 150 mgm given twice a day. However, when the dose exceeds 300 mgm twice a day, the incidence of nausea and vomiting may be serious enough to prohibit the use of this dose. Consequently, the best therapeutic schedule is 150 mgm given every 12 hours.

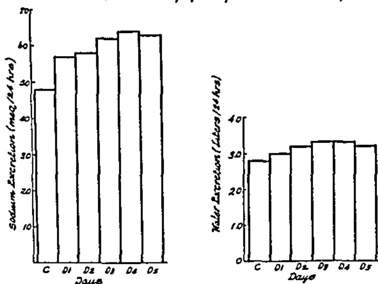


Figure 52. The effect of chlorazanil on sodium and water excretion (After Ford, Rochelle, Spurr, Handley and Moyer (32) Courtesy *Am. J. Cardiology*).

An increase in the blood urea nitrogen and plasma creatinine has been observed in some patients. At the same time, the urinary excretion rate of urea ususally increases. The BUN in these patients returned to normal immediately when the drug was discontinued. These observations suggest that increase in BUN is not a result of renal damage, but rather may be due to an increased rate of urea formation.

TABLE XVIII

EFFECT OF CHLORAZANIL ON WATER AND ELECTROLYTE EXCRETION (After Ford, Rochelle, Handley and Moyer (32), courtesy *Am J Cardiology*)

(Average values for 8 dogs)

	Urine Flow cc/min.				*Urine Sodium μEq/min*				*Urine Potassium μEq/min*			
	C	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3
Given 8 mgm/kgm intravenously												
Mean	0.2	0.5	0.7	0.7	6	66	110	109	6	14	7	9
Per cent of control		250	350	350		1100	1833	1817		233	117	150
p value		0.05	0.01	0.05		0.05	0.05	0.01		0.20	0.50	0.50

C = Control
D_1 = First 20 minutes after drug
D_2 = Two hours after drug
D_3 = Four hours after drug

Chapter 9

THE PHARMACOLOGY AND CLINICAL USE OF ACID-FORMING AGENTS

AMMONIUM and calcium salts produce acidosis since they yield an excess of anions on ingestion. Ammonium chloride and nitrate, calcium chloride and nitrate, and even hydrochloric acid have been used to produce acidosis and promote diuresis. Of the group, ammonium chloride is the only one that remains in general use. Calcium salts have disagreeable tastes and produce a high incidence of gastrointestinal irritation. Hydrochloric acid is seldom used because of problems involved in administration. More recently, insoluble cation exchange resins have been employed to produce acidosis. They tend to remove fixed base from body reservoirs unaccompanied by anions. The cation exchange resins are not popular because of the large amounts that must be administered to be effective

Mechanism of action. After absorption, the ammonia ion of ammonium salts is converted to urea by the liver. The anions released remove base from bicarbonate The resulting decrease in the ratio of bicarbonate to carbonic acid causes acidosis (36) Acidosis from calcium salts is due to limited absorption of calcium ions from the intestinal tract, where they are largely precipitated as the carbonate or phosphate, or as soaps by combining with fatty acids An excess of anion is absorbed and produces acidosis (37, 41).

The nitrates have been claimed to be more potent diuretics than the chlorides, but it is improbable that the anion has any specific diuretic effect (52).

Ammonium chloride and the other acid-forming salts do not produce diuresis by an osmotic effect in the renal tubule. The combined osmotic effect of the urea formed from the ammonium ions and the excess chloride is not large enough to produce osmotic diuresis. Furthermore, when the acidosis subsides, as it eventually does, even though the administration of the acidifying salt is continued, the diuresis terminates.

One proposed explanation for the diuresis during acidosis is that the water and base binding capacity of the tissue proteins is reduced. This effect is presumed to cause a movement of cellular and interstitial water and electrolytes into the circulatory system which results in renal excretion. Some doubt has developed that acidosis as such is responsible for diuresis and the potentiating effect of acid-forming salts on mercurial diuresis. It has been observed that lowering the blood pH by breathing 7 per cent carbon dioxide failed to potentiate mercurial diuresis while a comparable pH obtained with ammonium chloride was effective (1). One must conclude from the available information that the mechanism of diuresis of the acidosis producing agents has not been established.

Effect of electrolyte excretion. During the first 24 hours, the increased rate of chloride excretion is followed by the excretion of nearly an equivalent amount of sodium derived from blood buffers. Were this process to continue, a dangerous degree of acidosis would develop. Several compensatory mechanisms for base conservation promptly come into action, preventing such a condition from occurring.

These mechanisms progressively decrease the rate of sodium excretion after the first day of ammonium chloride administration so that at the fifth or sixth day a positive balance is attained. An increase in the renal tubular reabsorption of sodium and chloride from the filtrate restricts the loss of these ions. In addition, this serves to maintain a relatively constant total ionic concentration despite a reduced bicarbonate concentration. A shift of potassium and calcium *from the tissues to the blood and increased urinary excre-*tion of these ions conserves some sodium.

The renal production of ammonia and titratable acid is the one mechanism that ultimately results in complete compensation and restoration of fixed base despite continued administration of acid-forming salts. Ammonia formation occurs in the renal tubular cells from the deamination of glutamine and other amino acids. A reduced urinary pH is believed to stimulate the ammonia forming mechanism. *Normal kidneys under stress can produce* about 390 mEq (7gm) of ammonia per 24 hours. An equivalent amount of base is thus conserved. In heart failure and nephritis, the ammonia-producing mechanism is depressed. Acidosis and the degree of diuresis are greater and more prolonged than in individuals that do not have cardiovascular renal disease. The rate of formation of ammonia increases progressively during acidosis until a positive fixed base balance occurs. When balance is restored, the diuretic action of acid-forming substances terminates (Figure 53).

Since the effectiveness of acidifying agents depends upon the lag in ammonia formation by the kidney, acidosis must be induced rapidly. Administration of 9 gm of ammonium chloride results in a positive fixed-base balance on about the fifth day. If the dose is increased to 15 gm

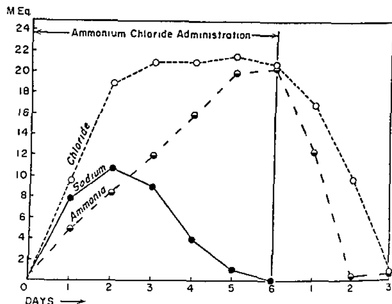


Figure 53 The effect of ammonium chloride on the excretion of chloride, sodium and ammonia in a normal subject Nine grams of ammonium chloride were administered daily in divided doses for 6 days. (After Drill (20), courtesy *Pharmacology in Medicine*, V A. Drill, Ed., Blakiston Div , McGraw-Hill Book Company)

daily, balance is delayed until about the ninth day.

It is apparent from the compensatory mechanisms that develop during diuresis from the acidifying agents that these substances must be used in cycles to produce effective diuresis. Once the ammonia-forming mechanism has produced complete compensation, these agents must be discontinued for several days.

Toxicity. Gastric irritation with nausea and vomiting is the most common side effect from ammonium chloride. In advanced liver disease, ammonium chloride should not be administered. When the liver is damaged, the capacity

to convert ammonia to urea is greatly depressed and ammonia poisoning may occur. Methemoglobin is a complication sometimes encountered with ammonium nitrate as a result of the bacterial conversion of nitrate to nitrite in the intestinal tract.

Potentiation. When used in combination with mercurial diuretics, ammonium chloride produces a potentiation and not a simple additive effect. In the absence of hypochloremia, there is not any explanation for the phenomena. When hypochloremia and loss of diuretic action develops from a mercurial diuretic, responsiveness may be restored by ammonium chloride. Mercurial diuretics tend to deplete the plasma chloride, especially in patients with severe cardiac failure. When this occurs, ammonium chlo-

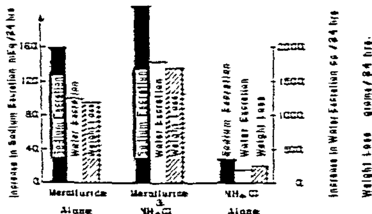


Figure 54A. Diuretic response to meralluride before and after the administration of ammonium chloride (average values for 10 patients with heart failure).

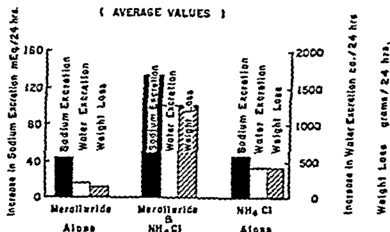


Figure 54B. The same treatment in 2 patients with hypochloremic alkalosis (average values).

ride may be effective in restoring responsiveness to mercurial diuretics (Figure 54A, B). As the plasma levels of chloride increase toward normal, the diuretic response to mercurials progressively increases. A minimum of 2 grams given with each meal should be used for this purpose.

When ammonium chloride is given prophylactically to prevent the hypochloremia associated with mercurial administration, it should be administered at least 12 hours before the mercurial is given.

When patients who are in severe heart failure require parenteral mercurial administration more frequently than once a week, *it is usually proper to give* ammonium chloride for at least 24 hours before and 12 hours after the administration of the mercurial as a prophylactic measure

against the development of hypochloremic alkalosis. If used for this purpose, one gram with each meal is adequate. When necessary to administer the mercurial as often as 3 times a week, ammonium chloride should be administered daily in order to prevent chloride depletion.

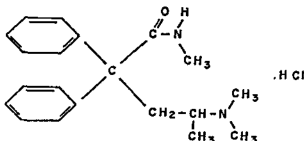
The possibility of the development of serious acidosis must be kept in mind when administering ammonium chloride to any patient with primary renal disease. Lethargy, nausea, and weakness are prominent symptoms Hyperpnea becomes prominent with advanced acidosis. Blood chemistry studies show a high chloride and a low CO_2 with normal sodium.

Chapter 10

PHARMACOLOGY AND CLINICAL OBSERVATIONS ON VALERAMIDE AND STEROID DIURETICS

THE DIURETIC ACTIVITY of alpha, alpha-diphenyl gamma-dimethyl N-methyl valeramide hydrochloride has been investigated in animals and patients with mild congestive heart failure (48). The original investigation was done on the racemic mixture (U-3772) of the compound but later the d-isomer (U-6420) was added to the study since it appeared to be somewhat more active in rat assays. This compound is noteworthy because it is a potent oxytocic, has some degree of cholinergic blocking action, as well as having diuretic action.

Chemistry. The compound is a water and ethanol soluble white crystalline material with the following structure:



Mechanism of action. The mechanism by which this compound produces diuresis is unknown. Changes in renal

hemodynamics in dogs are minimal. A tendency for a slight increase in renal plasma flow during the first thirty minutes after administration of the compound is observed but no significant changes in glomerular filtration rate occur. The compound produces a slight depression of mean blood pressure immediately after intravenous injection that persists for at least two hours.

Intravenous dosages of 5 to 10 mgm per kgm of the racemic mixture increases both urine volume and the rate

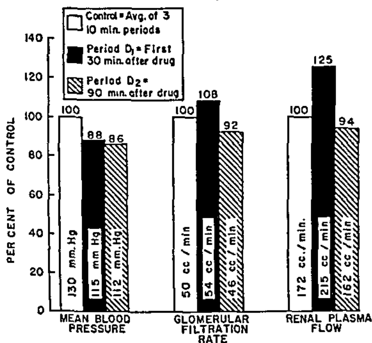


Figure 55 Renal hemodynamic response to intravenous U-3772. Average values for 8 dogs (10 mgm/kgm).

of sodium excretion. The effect of the compound on potassium excretion is minimal and variable. Diuresis, when it occurs, develops within 20 to 30 minutes after intravenous administration of the compound.

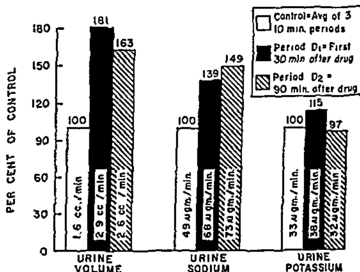


Figure 56. The effect of U-3772 on water and electrolyte excretion Average values for 8 dogs (10 mgm/kgm, I.V.).

Although the d-isomer is a more potent diuretic in the rat than the racemic mixture, it was less effective in the nonhydrated dog.

Clinical observations. *The oral administration* of 250 mgm of the racemic mixture to patients with mild congestive heart failure that had been controlled by other therapy did produce a slight degree of diuresis and natriuresis. However, the severity of *the side effects* made *it impossible*

TABLE XIX

EFFECT OF U-3772 & U-6420 ON SODIUM EXCRETION IN PATIENTS WITH MILD HEART FAILURE

Patient	Dose of Drug mgm/24 hrs	Sodium Excretion Control	mEq/24 hrs. Drug	Urine Volume Liters/24 hrs. Control	Urine Volume Liters/24 hrs. Drug	Side Effects
Response to U-3772*						
1	250	45	55	2.3	2.5	Bladder cramps, sphincter spasms, and urinary retention
2	250	50	60	3.1	3.1	Bladder cramps, sphincter spasms, and urinary retention
3	250	45	55	3.0	3.2	Bladder cramps, sphincter spasms, and urinary retention
Response to U-6420**						
1	450	48	72	2.8	3.2	Slight bladder cramps
2	450	52	73	3.1	3.3	Bladder cramps and urinary retention
3	450	43	80	2.8	3.0	Slight bladder cramps
4	450	45	85	3.0	3.0	None
5	450	45	75	3.3	2.9	None
6	900	45	80	2.6	3.1	Severe bladder cramps, sphincter spasm and urinary retention
7	900	46	82	2.2	3.3	Severe bladder cramps, sphincter spasm and urinary retention
Mean		46	78			
% of control			170			

Key: * Study discontinued after 3 patients were observed due to untoward side effects
** Study discontinued after 7 patients were observed due to untoward side effects

to study the compound for more than a few days in a small number of patients (Table XIX).

The d-isomer was somewhat better tolerated than the racemic mixture and larger doses could be administered. A significant increase in sodium excretion was noted in all seven patients receiving 450 to 900 mgm of the drug. The 900 mgm dose was no more effective than 450 mgm. A significant increase in urine volume was noted in 5 of the 7 patients. After several days of treatment with the compound, side effects began to appear and the study was terminated (Table XIX). Many of the side effects, such as vesicle sphincter spasm, and bladder cramps, are undoubtedly related to the cholinergic blocking action of these compounds.

ANTI-ALDOSTERONE COMPOUNDS

The development of compounds that competitively block the effect of mineralocorticoid actions may be a fruitful new approach to diuretic therapy. Interest in agents of this type has developed because of the discovery that increased amounts of salt-retaining steroids, particularly aldosterone, are found in the urine in various types of edema (53). Aldosterone is the most potent salt-retaining steroid produced by the adrenal cortex that has been discovered Increased amounts of this steroid are found in the urine of patients with congestive heart failure, toxemia of pregnancy, liver cirrhosis, and other diseases associated with edema and hypertension. If increased aldosterone excretion is a contributory factor to edema formation in these conditions, a compound that blocks the action of this steroid might be expected to cause diuresis.

Recently, a 17-spirolactone steroid derivative has been

reported to block the sodium retention from desoxycorticosterone and aldosterone in animals. A limited trial in patients with congestive heart failure and edema indicates that the compound is capable of producing diuresis and increased sodium excretion (21).

Chapter 11

SUMMARY OF THE CLINICAL USE OF DIURETICS

CONGESTIVE HEART FAILURE

DIURETIC AGENTS, as important as they may be, are only one aspect of the treatment of patients with abnormal sodium and water retention. The use of diuretics is not a curative measure, but rather these agents improve only the symptoms associated with edema formation. Consequently, when possible the basic physiological defect should be corrected. With the advent of potent and safe diuretics, attention has been directed more and more toward the defective excretion of sodium in congestive heart failure. Since renal retention of sodium and water is a secondary effect, digitalis and restricted physical activity are of prime importance. Diuretics are indicated when these more simple measures fail or when the condition demands their use.

The authors feel that it is important to make certain that effective therapy is used rather than risk under treatment. This is especially true when one considers that many more patients develop severe and progressive heart failure from inadequate therapy than get into difficulty from the side effects associated with over treatment. Diuretics are the primary therapeutic measure for heart failure associated with such conditions as infections, toxic myocarditis, cor pulmonae, and mitral stenosis.

In advanced cardiac failure, exercise reduces the glomerular filtration rate below a critical level which may contribute to the renal retention of sodium and water. Increasing the glomerular filtration rate or reducing tubular reabsorption of sodium and water will correct this tendency toward fluid accumulation. Some improvement in renal functions may occur with bed rest. Glomerular filtration rate is highest when the patient is supine and decreases as the upright position is assumed Continued exercise tends to produce a progressive reduction in glomerular filtration. Aside from reducing the burden on the heart, the improvement in renal function frequently observed during bed rest is a valuable therapeutic adjunct for patients in heart failure. In non-cardiac edema, complete bed rest is rarely indicated.

Bed rest for the treatment of heart failure should be viewed as a temporary measure only, since many secondary physiological alterations follow prolonged bed confinement. Nevertheless, restricted physical activity should be advised as a permanent measure. Once heart failure has developed, it is rare that cardiac function returns entirely to normal, irrespective of the etiology of the disease or the therapeutic program instituted. Moreover, the more frequently and more severely a patient decompensates, the more difficult it is to improve cardiac function to a condition even approaching normal.

Sodium chloride intake should also be given primary consideration in patients with edema. Water intake is of little importance so long as sodium intake is rigidly restricted. In fact, a large urinary volume tends to promote an increase in sodium excretion. When a patient has been on a low salt intake for a period of time, the body becomes relatively depleted of sodium. Consequent-

ly, such patients are quite vulnerable to excessive sodium loss such as may occur in diarrhea or vomiting.

Generally, the more severe the heart failure, the less salt can be excreted by the kidney. Thus, in a patient with mild heart failure, restriction of salt intake need not be drastic. The avoidance of salty food, removal of salt from the table, and avoiding the use of salt in cooking is frequently adequate. In moderately severe heart failure, the salt intake should be restricted to less than 500 mgm of sodium per day. (See pages 174-177 for low sodium diets.)

When effective diuretics are given continuously, the salt intake can usually be liberalized. The family and the patient should be instructed in the methods of preparation and virtues of a low salt diet by someone adequately trained in this field. This cannot be emphasized too much, since many patients have no conception of the types of foods that should be used and methods for preparing low salt diets.

As cardiovascular deterioration proceeds, the patient in heart failure may become unresponsive to therapy even though plasma electrolytes are within normal limits. Under these circumstances, mercurials given in combination with other agents may be effective. The rationale for this procedure is the assumption that different diuretics act by different mechanisms. When 2 cc of meralluride produces inadequate diuresis, the dose should be increased to as much as 4 cc. If this dose proves ineffective, 0.5 grams of aminophylline given intravenously one hour after the mercurial may initiate diuresis. Such a drug combination may be superior to larger doses of the mercurials and may prevent mercurial accumulation in the body, particularly in patients with oliguria.

Single injections of mercurials are indicated follow-

ing acute pulmonary edema, acute left ventricular failure, and in edema associated with heart failure of short duration. When it becomes apparent that repeated administration of a parenteral mercurial is indicated, the drug should be given as infrequently as possible. The smallest dose that will maintain the patient at "dry weight" and in a state of maximum compensation should be ascertained. It is inadvisable to withhold diuretic therapy until beginning decompensation with a considerable weight gain has occurred. Certainly, patients feel better when large fluctuations in weight are avoided. It is usually unwise to have a patient lose more than 5 pounds at each dose of the diuretic when receiving maintenance therapy.

When the response to parenteral mercurials is not adequate, ammonium chloride will frequently increase the responsiveness, particularly if the patient is in a state of hypochloremic alkalosis. Ammonium chloride may be prescribed in a dose of 1 gram with each meal about 24 hours before and 12 hours after the injection of mercurials as prophylaxis against hypochloremia. This type of prophylaxis is especially important if mercurials are given more often than twice weekly.

Decholin (20 per cent) in doses of 5 to 10 cc has also been reported to be effective for increasing mercurial responsiveness. The authors have observed such apparent responses but the results have been very erratic and unpredictable. Certainly, neither an additive nor a synergistic effect of Decholin on responsiveness to mercurial diuretics can be demonstrated in the usual patient with heart failure

Chlorothiazide given in combination with mercurials produces an additive response in patients who are not adequately responsive to mercurials This effect has also

been observed in mercurial resistant patients. Frequently, patients unresponsive to mercurials will obtain adequate diuresis from chlorothiazide alone.

Ultimately, failure to respond to mercurials will be due to progressive impairment of glomerular filtration to such a degree that little water and sodium is filtered. Under these conditions, virtually all of the water and sodium is reabsorbed, even after maximal tubular depression with mercurials. Occasionally, patients fail to respond to diuretics because of an electrolyte imbalance. This complication may be caused by too vigorous diuretic therapy and too rigid salt restriction or progressive myocardial degeneration. Four electrolyte imbalance states have been observed: (1) chronic dilutional hyponatremia, (2) hypochloremic alkalosis, (3) salt depletion syndrome, and (4) potassium deficiency.

Chronic dilutional hyponatremia is one of the most serious electrolyte derangements and is apparently unrelated to treatment, unless concurrent primary renal disease is present. Under the latter circumstances, if fluids of low sodium content are given in excess of the kidney's ability to excrete water, dilutional hyponatremia result. The syndrome results from extreme dilution of extracellular fluid. In the absence of severe primary renal disease in patients with heart failure, the syndrome is indicative of extensive myocardial impairment. Both serum sodium and chloride are low although total body sodium is excessive. Prognosis is poor and attempts at replacement therapy seldom are successful.

Hypochloremic alkalosis and salt depletion syndrome occur as a complication of vigorous mercurial therapy and rigid salt restriction. In hypochloremic alkalosis the main *deficit is chloride*. *In salt depletion syndrome,*

it is sodium. Clinically, in both conditions, there is lassitude, apathy, anorexia, oliguria and no response to mercurial diuretics. Hypochloremic alkalosis is also usually indicative of severe myocardial disease. It is difficult to produce this syndrome in normal subjects or patients with only mild heart failure, even with vigorous daily mercurial diuretic administration.

Therapy of hypochloremic alkalosis is directed at replacement of the appropriate electrolyte using oral ammonium chloride or a 2 per cent solution given intravenously. It is preferable to give the drug orally unless the patient is in extremis. For oral replacement, at least 2 grams (30 grains) should be given every 4 hours The drug is best given after meals in order to avoid nausea and vomiting. Hypochloremic alkalosis can easily be avoided by giving ammonium chloride concurrently with the administration of mercurial diuretics to patients with severe myocardial disease.

The sodium deficit in patients with hyponatremia may be calculated from the serum sodium values and replacement is based on such calculations We prefer to base our calculations on extracellular (including intravascular) fluid sodium concentrations and to use 5 per cent sodium chloride for replacement therapy The volume of extracellular fluid is approximately 20 per cent of body weight (kilograms). Plasma sodium concentration is approximately equal to extravascular, extracellular fluid sodium concentration Therefore, normal plasma sodium minus the measured plasma sodium (milliequivalents) in the patient multiplied by the extracellular fluid volume (20 per cent of body weight) equals the amount of sodium (in milliequivalents) required to correct the deficit. One

cc of 5 per cent sodium chloride equals 0.85 milliequivalent. Therefore:

$$\frac{\text{Body Weight (kgms)} \times 20 \times 140 - (\text{patient's plasma sodium in mEq})}{0.85} =$$

cc of 5 per cent sodium chloride to be administered

The solution should be given slowly by intravenous infusion over a period of 2 hours or more. Fluids should be restricted (especially water) while the 5 per cent sodium chloride is being given and for some time thereafter, otherwise the plasma sodium will again be diluted, the blood volume increased and the heart failure aggravated After allowing about 12 hours for equilibrium and stability to occur, the plasma sodium concentration should again be determined. The process must then be repeated if the hyponatremia has not been corrected. It is unnecessary, in our opinion, to attempt to bring the sodium concentration entirely to normal. Only if the sodium level is below 125 to 127 mEq is corrective therapy indicated, then only if the clinical symptoms demand it (severe oliguria, extreme weakness and lethargy, and cerebral symptoms). If no symptoms are present, a liberalized salt intake will suffice. After the syndrome is corrected, the patient is then treated as a severe cardiac, employing bed rest, digitalis, and diuretics as before.

Potassium deficiency is another complication of diuretic therapy. Digitalis toxicity may be precipitated by hypokalemia. Clinically extreme muscle weakness, cardiac irregularities and abdominal distention are clues that should lead to the diagnosis. Ingestion of 6 to 8 ounces of orange juice on the day of mercurial administration is usually adequate insurance against this complication. Should potassium deficiency occur, oral potassium chloride in doses of 2 to 5 grams daily is indicated.

Hypokalemia may also occur from intensive therapy with chlorothiazide and the carbonic anhydrase inhibitors. The latter agents, if given continuously, reduce plasma bicarbonate and cause acidosis.

TABLE XX

SUMMARY OF METHOD OF ADMINISTRATION & OBSERVATIONS ON DIURETIC POTENCY ON SOME OF THE MORE IMPORTANT DIURETICS STUDIED BY THE AUTHORS

Type of Diuretics	*Specific Drug*	*Method of Administration*	*Potency Estimation*	*Dose*
Organomercurials	meralluride (Mercuhydrin)	Parenteral	1.0	1 to 2 cc as needed to keep patient at "dry weight"
	chlormerodrin (Neohydrin)	Oral	0.5	1 to 2 tablets four times a day after meals
	mercaptomerin (Thiomerin)	Parenteral	0.6	2 cc as needed to keep patient at "dry weight"
	mercumatilin (Cumertilin)	Oral	<0.5	1 to 2 tablets four times a day — not very effective
	mercurophylline (Mercupurin)	Parenteral	—	2 cc as needed
	WY 1204 (Oradon)	Oral	0.7	1 to 2 tablets four times a day
Carbonic anhydrase inhibitors	acetazoleamide (Diamox)	Oral	0.5	250 mgm daily for 3 days out of each week
	ethoxzolamide (Cardrase)	Oral	0.5	250 mgm daily for 3 days out of each week
Xanthines	aminoisometradine (Rolicton)	Oral	0.5	1-2 tablets given 4 times a day
	aminometradine (Mictine)	Oral	0.7	1-2 tablets given 4 times a day
	aminophylline	Parenteral	<0.5	500 mgm every 4 hours as needed
Acidifying salts	Ammonium chloride (*Alone*)	Oral	<0.50	2 gm 4 times a day
Chlorothiazide	chlorothiazide (Diuril)	Oral	0.8	500 to 1000 mgm 1-3 times a day
	chlorothiazide (Diuril)	Parenteral	<0.5	Same as oral

Potency Estimation — Comparative response in sodium excretion using meralluride (Mercuhydrin) as "1"

SUMMARY OF DIURETIC THERAPY FOR SPECIFIC DISEASE ENTITIES

A. Congestive Heart Failure. Since the primary defect in congestive heart failure is inadequate cardiac output, every effort should be made to restrict the patient's activities. The judicious use of a cardiac glycoside is indicated Diuretics may be employed as follows:

1. A parenteral mercurial diuretic initially when heart failure is severe, e g, meralluride (Mercuhydrin) 2 cc intramuscularly or mercaptomerin (Thiomerin) 2 cc subcutaneously daily for 3 to 5 days until gross edema has disappeared

2. Chlorothiazide (Diuril), 1000 mgm every 8 to 12 hours after the emergency is controlled. The dose is gradually decreased to the minimally effective dose but no less than 500 mgm daily should be given.

3. Chlormerodrin (Neohydrin), 4 to 8 tablets daily for maintenance of edema-free state if the response to chlorothiazide is not adequate.

When heart failure is mild, compensation may also be maintained with acetazoleamide (Diamox) or ethoxzolamide (Cardrase), 250 mgm daily for 3 consecutive days out of each week In moderate to severe heart failure, Diamox will rarely be adequate for maintenance therapy. Chlorothiazide (500 to 1000 mgm b.i d.) or Neohydrin (1 to 2 tablets after each meal and at bedtime) must be used if the oral route of drug administration is to be employed, in such cases Otherwise, parenterally administered mercurial agents must be given in adequate doses (1 to 4 cc) * and as frequently as necessary to maintain the edema-free state and full cardiac compensa-

tion. Parenteral diuretic therapy may become necessary if gross edema reappears.

*Doses in excess of 2 cc are employed only in patients with intractable heart failure

B. Premenstrual Edema. Edema is not marked in this condition but the symptoms may be annoying. The following prophylactic treatment may be used:

1 On last 5 to 7 days of the menstrual cycle with the onset of subjective tension place on a low sodium diet Administer chlorothiazide (Diuril) in a dose of 500 mgm twice a day, or 250 mgm of acetazoleamide (Diamox) (1 tablet) daily, or 4 to 8 tablets of chlormerodrin (Neohydrin) daily.

C. Edema of Pregnancy. Since pre-existing disease may be responsible for edema in this condition, a close medical survey must be completed. Therapy may be summarized as follows:

1. At first sign of edema, place on a low sodium diet.
2. If not controlled by diet alone, administer 4 to 8 tablets of Neohydrin daily or chlorothiazide 500 to 1000 mgm twice daily or 250 mgm of acetazoleamide (Diamox) every other day if edema is not marked

D. Nephrotic Syndrome. Multiple factors are operative in this condition and include excessive urinary protein loss, decreased glomerular filtration, and increased tubular reabsorption of sodium. The treatment may be summarized as follows:

1. Bed rest.
2. Low sodium diet.

3. Chlorothiazide, 500 to 1000 mgm b.i.d.

4. If the above procedures do not control edema in one week, a 7-day trial of corticotropin may be instituted. Twenty-five units of ACTH in 1000 cc of 5 per cent dextrose given intravenously over an eight hour period daily or as corticotropin gel, 40 units intramuscularly, may be tried. Alternatively, prednisone may be used in a dosage schedule of 10 mgm every 6 hours for 4 doses, then 5 mgm every 6 hours for 8 doses, then 5 mgm every 12 hours for 8 doses. Diuresis ususally occurs as the steroid (or ACTH) therapy is withdrawn. The mechanism is not understood.

5. If no response to above therapy, administer 100 mgm of salt-poor human albumin intravenously every other day. This is an expensive procedure.

6. Finally, parenteral mercurials may be tried if edema is severe.

E. Hepatic Disease. Since the edema usually originates from inadequate protein formation with reduction in blood protein osmotic pressure, the underlying liver disease should be attacked therapeutically. However, other factors such as decreased hepatic inactivation of salt-retaining steroids may be treated by agents acting to block the renal tubular reabsorption of sodium. An outline of treatment of the edema of hepatic disease follows

1. Low sodium diet.

2. Chlorothiazide, 1000 mgm twice a day.

3. In presence of significant hypoalbuminemia (serum albumin less than 2 gm per cent) use salt-poor human albumin 100 gm intravenously every

other day to achieve diuresis. The expense may be a contraindication here.

4 If inadequate response to intravenous albumin or chlorothiazide is obtained, Mercuhydrin in a daily dose of 2 cc intramuscularly may be tried.

5 After massive edema is controlled, Neohydrin in a daily dose of 4 to 8 tablets may be used for maintenance.

F. Iatrogenic Steroid Edema. In the treatment of certain severe diseases, excessive dosages of corticotropin, cortisone or prednisone may be required When sodium retention and edema become a problem, it is preferable to discontinue the steroid but this is not always possible. The edema can usually be controlled by daily administration of chlorothiazide in a dose of 1000 mgm every eight hours, or chlormerodrin in a dose of 2 tablets 4 times a day If these agents are not adequate when given alone, they should be used in combination

H. Hypertension.

1. Chlorothiazide, 250 to 500 mgm b.i.d.
2. Continue chlorothiazide and add drugs which depress sympathetic nervous system activity as indicated in order to return blood pressure to normal.

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ADDENDUM

The therapeutic effectiveness of chlorothiazide has prompted an evaluation of other benzothiadiazine derivatives in an attempt to find compounds with greater potency and a lower incidence of side effects. Figure 1 presents the

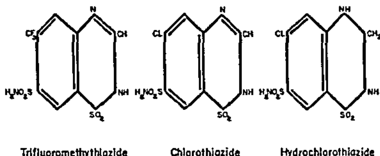


Figure 1. Structural formulae of chlorothiazide, hydrochlorothiazide, and flumethiazide.

structural formula of two new agents which have been studied most thoroughly i.e., trifluoromethylthiazide (Flumethiazide) and hydrochlorothiazide (Hydrodiuril).

An evaluation of the effects of flumethiazide administered orally revealed similar responses in renal hemodynamics as observed with the administration of chlorothiazide. There was no change in mean blood pressure in any patients throughout the study. There was no significant reduction in either renal plasma flow or glomerular filtration rate. However, there was a marked increase in sodium excretion which occurred within the first two hours after drug administration and reached its maximum effect within two to four hours. The duration of activity appeared to be

effective dose was approximately 1000 mgm given twice a day. Doses in exces of this amount produced very little additional diuretic or natriuretic response.

Hydrochlorothiazide was studied after both intravenous and oral administration. This agent was more potent than chlorothiazide at equal doses. The dosage ratio for the production of the same increase in sodium excretion was approximately 1:10 comparing hydrochlorothiazide and chlorothiazide. However, at the maximum natriuretic and diuretic effect of each drug, hydrochlorothiazide produced no greater increase in sodium excretion than was observed following the administration of chlorothiazide (Figure 2). The maximum effective dose of hydrochlorothiazide was approximately 100 mgm given twice a day. Increasing the dose above the amount produced very little additional natriuretic effect

When 200 mgm of hydrochlorothiazide was given intra-

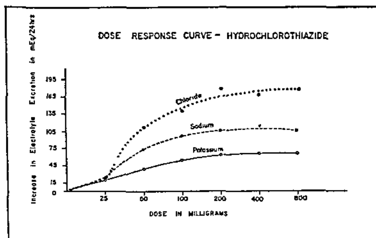


Figure 3 Dose response curve of hydrochlorothiazide measuring chloride, sodium and potassium excretion The primary effect was an increase in chloride excretion

eight to twelve hours. At equally potent natriuretic doses there seemed to be less increase in potassium excretion than was observed under similar circumstances when chlorothiazide was administered.

Using weight loss as the measure of response in patients with cardiac failure who had edema, and using sodium excretion in non-edematous patients, the dose response curve was approximately the same as that observed following the administration of chlorothiazide when both drugs were given by the oral route. It appeared that the maximum

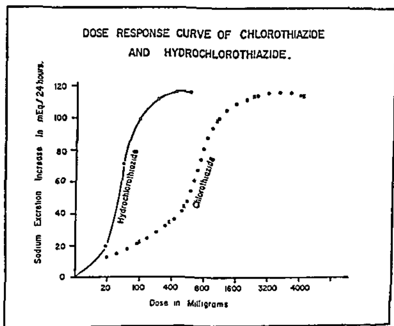


Figure 2. Dose response curves for chlorothiazide and hydrochlorothiazide using the increase in sodium excretion as the basis for estimating potency. Hydrochlorothiazide showed the same dose response curve, as was observed following the administration of chlorothiazide, at about one tenth the dose. The maximum response obtainable was about the same for each of the drugs.

APPENDIX

SODIUM RESTRICTED DIETS USED AT THE HAHNEMANN HOSPITAL OF PHILADELPHIA*

The diet should contain:

Calories: 2000 (or as indicated)

Protein: 70 grams

Minerals and vitamins: Adequate to meet the recommended dietary allowances.

1000 mgm (1 gram) sodium diet

Dietary restrictions as follows:

All food is prepared without the addition of salt.

Baking powder, baking soda and foods with a high natural sodium content are excluded from the diet (find list on following pages).

Salt-free bread is included in this diet.

Protein foods are restricted. Most protein foods are naturally high in sodium; therefore, the daily intake is limited to the basic requirements:

Meat, fish, poultry	5 ounces
Egg	1
Milk (regular)	1 pint only

500 mgm (0.5 gram) sodium diet

This diet is the same as the 1 gram sodium diet with the exception of the use of salt-free butter and the omission of the following vegetables:

Beets
Carrots
Celery
Spinach

* Drawn up by Mrs. Marie Bauer

venously, there was a temporary reduction in glomerular filtration rate but this returned to control levels within one hour. Natriuresis and diuresis began in one hour after drug administration and lasted in excess of twelve hours.

The electrolyte excretion pattern showed a greater effect on the increase of chloride excretion when either sodium or potassium. In fact there was a greater kaluretic effect than was previously observed with chlorothiazide in equal natriuretic doses. The increase in chloride excretion was approximately the same as the increase in sodium excretion plus the increase in potassium excretion in milliequivalents (Figure 3).

The clinical response of these agents was observed in the 48 hour weight loss experienced in a group of patients with congestive heart faliure. It was shown that the weight loss in these patients was the same when the maximum effective dose of chlorothiazide, hydrochlorothiazide, and flumethiazide were given.

SODIUM RESTRICTED FOOD LIST (Continued)

FOOD	*ALLOWED*	*AVOID*
Fruit	Fresh, frozen, canned or dried unless label states artificial color, flavor or sodium preservative added. Apples, apple juice, applesauce, apricots, avocado, banana, blackberries, cherries, chestnuts, cranberries, red currants, dates, figs, gooseberries, grapefruit, grapes, grape juice, kumquats, lemons, apple cider, limes, mulberries, nectarines, oranges, orange juice, peaches, pears, pineapple, persimmons, pineapple juice, plums, prune juice, pomgranate, quince, raspberries, rhubarb, strawberries, tangerines	Any fruits having sodium preservatives added, melons.
Meat, Fish	Lean beef, white turkey, white chicken, duck, goose, lamb, heart tongue, quail, rabbit, sweetbreads, tripe, lean veal, pork liver, calf liver, one time a week only. Fresh fish only, catfish, cod, halibut, salmon, sole and all fresh water fish.	Ham, bacon, salt pork, corned beef, corned pork, dried beef, kidney, brains, lunch meats, Kosher meats, canned meats, fish and poultry, lobster, shrimp, sausage, shellfish, frankfurters, frozen fish fillets and oysters
Potato or substitute	White potato, sweet potato, white rice, soybeans, plain macaroni, spaghetti, plain noodles.	
Seasonings	Allspice, almond extract, anise, basil, bay leaf, caraway, cardamon, chives, cinnamon, cloves, coriander, curry, dill, fennel, garlic, ginger unprepared horseradish, leeks, lemon juice extract, mace, maple extract, marjoram, mint, dry mustard, nutmeg, onion juice, orange extract, orange peel, oregano, paprika, parsley, pepper, peppermint extract, pimiento, poppyseed, poultry seasonings, rosemary, saccharin, saffron, sage, savory, sesame, tarragon, thyme, tumeric, vanilla extract and vinegar.	Salt, celery salt, onion salt, other seasoned salt, chili sauce, horseradish, meat sauces, soy sauce, prepared mustard, catsup, Worcestershire sauce

SODIUM RESTRICTED FOOD LIST

FOOD	*ALLOWED*	*AVOID*
Beverages	Coffee, tea, milk, Sanka, Postum, plain cocoa.	Softened water, butter, Dutch Process Cocoa, instant coffee and cocoa, malted milk, Ovaltine and regular milk except as allowed
Bread	Breads made of any flour (except self-rising) without salt and regular milk.	Regular bread, Graham crackers, soda crackers, self rising flour, and mixes; biscuit, muffins, waffles and pancakes
Cereals	Pearled barley, Cream of Wheat, Rolled Oats, Pettijohns, Cornstarch, Farina, Maltex, Ralston, Puffed Rice, Puffed Wheat, Cornmeal, Shredded Wheat, Muffets, Wheat Germ, Wheatena	Quick-cooking cereals, dry cereals except as listed
Cheese	Low sodium cottage cheese, low sodium American cheese	American cheese, cottage, cream cheese, sour cream, cheese spreads
Desserts	Plain gelatin, pie without salt in crust, Puddings cornstarch made with low sodium milk and egg allowance or egg yolk alone Cookies made without salt, baking powder (unless sodium free) or baking soda Cake made with low sodium milk, sodium free baking powder and no egg whites	Flavored gelatin, Junket tablets and the following commercial products ice cream, pudding mixes, bakery products, sherbert, cake mix, pie mix, and pretzels
Eggs	If on a 1 gram sodium or less and eggs are desired in cooking, use only egg yolks	
Fat	Sweet butter, unsalted margarine, vegetable shortening, salad dressings made with allowed foods Unsalted salad oils corn oil, olive oil, peanut oil, soybean oil, cottonseed oil, and vegetable oil.	Salted butter, bacon fat, salted margarine, salad dressings and mayonnaise

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SODIUM RESTRICTED FOOD LIST (Continued)

FOOD	*ALLOWED*	*AVOID*
Soup	Soups made with foods and seasonings allowed.	Bouillon cubes, canned soup, dehydrated soups, canned and dried meat extracts.
Sweets	White sugar, honey, jelly, jam with no preservatives, candy made with allowed foods.	Brown sugar, molasses, syrups, commercial candy.
Vegetables	Fresh, canned without salt, or frozen unless ordered otherwise Asparagus, green beans, wax beans, lima (baby) beans, corn, cowpeas, eggplant, endive, lentils, lettuce, okra, peas (not frozen), pumpkin, soybeans, squash, tomatoes, salt-free tomato juice. If 1 gram or over. beets, chard, carrots, celery, spinach.	Canned vegetables with salt, canned vegetable juices with salt, kale, artichokes, dandelion greens, mustard greens, sauerkraut, watercress, strongly flavored vegetables, frozen peas, succotash, mixed vegetables If under 1 gram. beets, celery, spinach and carrots.
Miscellaneous	Unsalted peanut butter, unsalted nuts, unsalted popcorn, chewing gum, mint jelly, compressed yeast, salt-free baking powder	Brewer's yeast, salted nuts, salted popcorn, potato chips, olives, pickles, relishes, anchovies, caviar, baking soda and baking powder

Note With the use of low-sodium milk, ice cream will be allowed once a week.

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